

# Pharmaceutical Dosage Forms: Parenteral Medications

Third Edition

Volume 1: Formulation  
and Packaging



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Edited by  
**Sandeep Nema**  
**John D. Ludwig**

# **Pharmaceutical Dosage Forms**

## **Parenteral Medications Third Edition**

### **Volume 1 Formulation and Packaging**

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## 5 Formulation development of small and large volume injections

Madhav Kamat and Patrick P. DeLuca

### INTRODUCTION

As described in the U.S. Pharmacopeia, USP-32/NF-27 (1), an injection is a preparation intended for parenteral administration and/or for constituting or diluting a parenteral article prior to administration. It is administered through the skin or other external boundary tissue, rather than through the alimentary canal, so that therapeutic substances, using gravity or force, can gain direct entry to a blood vessel, organ, tissue, or lesion. Parenteral products are required to meet pharmacopeial requirements for sterility, pyrogens, particulate matter, and other contaminants, and, where appropriate, contain inhibitors of the growth of microorganisms.

The USP (1) categorizes sterile preparations for parenteral use according to the physical state of the product as follows:

1. Liquid preparations that are drug substances or solutions thereof, for example, [drug] injection.
2. Dry solids that, upon the addition of suitable vehicles, yield solutions conforming in all respects to the requirements for injections, for example, [drug] for injection.
3. Liquid preparations of drug substances dissolved or dispersed in a suitable emulsion medium, for example, [drug] injectable emulsion.
4. Liquid preparations of solids suspended in a suitable liquid medium, for example, [drug] injectable suspension.
5. Dry solids that, upon the addition of suitable vehicles, yield preparations conforming in all respects to the requirements for injectable suspensions, for example, [drug] for injectable suspension.

Depending on the volume of injection in a package, the USP further designates injection, as either (i) small-volume injections or (ii) large-volume intravenous (IV) solutions. The term small-volume injection applies to an injection that is packaged in containers labeled as containing 100 mL or less. The large-volume IV solution applies to a single-dose injection that is intended for IV use and is packaged in containers labeled as containing more than 100 mL. Although the term sterile pharmaceutical is applicable to all injections (radiopharmaceuticals included), ophthalmic preparations, and irrigating solutions, this chapter emphasizes the formulation of injectable dosage forms.

### FORMULATION OF SMALL-VOLUME INJECTIONS

In terms of number, the small-volume injections constitute the vast majority of all the injectable products in the market - small and large-volume injections combined. Whereas, large volume injections are administered exclusively as IV infusion, the small-volume injectables can be given by IV as well as other routes, although dictated by the volume of injection, as described later.

The goal of formulation development is to have a product that addresses all four requisites of an ideal product from a patient point of view: It should be safe, efficacious, stable, and acceptable/tolerable. From the point of marketing and commercial economics, the product should be easy to manufacture, relatively easy to use or present, and should have optimum shelf life at convenient storage conditions, such as room temperature. Although the preferred goal of the formulation scientist is to develop an injectable formulation that is ready to use (such as an aqueous solution), a number of codependent factors must be carefully evaluated in determining the most appropriate type of formulation. These factors are a) Biopharmaceutical considerations, b) Solubility, and c) Stability.

Biopharmaceutical considerations are aimed at achieving the required drug concentration for pharmacological response and include the intended mode of administration, desired onset of action, and the dose required. The formulation - the drug itself and the excipients used - must be compatible with body tissues, particularly taking care of properties such as hemolysis potential, pain on injection, precipitation of the drug upon administration, etc. Sterility, lack of pyrogenicity, and absence of particulate matter are other important considerations from general safety point of view.

Solubility issues become important when the drug does not have sufficient water solubility to achieve the target concentration in the formulation at physiologically acceptable pH range of 3-10. Various solubilization strategies must be employed to increase the solubility to achieve the required deliverable dose in a minimum possible volume. These techniques include use of buffers, salt formation, use of cosolvent, use of surfactants, etc.

Stability considerations are aimed at developing a formulation that provides sufficient shelf life, which is generally considered to be the time for 10% degradation. The product is optimized in such a way that its intrinsic degradation pathways, for example, the commonly encountered hydrolysis or oxidation, are minimized by appropriate modification of formulation composition, many times by using added substances, such as buffers, chelating agents, etc.

The successful formulation of an injectable small-volume preparation requires knowledge and expertise to effect rational decisions regarding the selection of

1. a suitable vehicle (aqueous, nonaqueous, or cosolvent),
2. added substances (buffers, antioxidants, antimicrobial agents, buffers, chelating agents, tonicity contributors, etc.), and
3. the appropriate container and closure components.

During the course of product development, formulation optimization is an iterative process and evolves as the product moves from the discovery to clinical to commercial stages. Inherent in the above decisions is the obligatory concern for product safety, effectiveness, stability, and reliability. As the injection formulation is finalized, a number of additional supportive studies must be undertaken to establish ruggedness of the formulation.

The majority of parenteral products are aqueous solutions, preferred because of their physiological compatibility and versatility with regard to route of administration. Survey of USP (1) shows that out of >300 pharmacopeial injection entries, nearly 70% are aqueous formulations (a similar trend is expected for nonpharmacopeial products as well). However, cosolvents or nonaqueous substances are often required to affect solution and/or stability of many compounds. Furthermore, for some other compounds, the desired properties must be attained through the use of an alternate dosage form such as suspension, emulsion, or even newer approaches such as liposomes and nanosuspensions.

Although each of these dosage forms have distinctive characteristics and formulation requirements, certain physical-chemical principles are common. Those common principles will be discussed in a general manner and the differences distinctive of each system will be emphasized. It is important to recognize that the pharmaceutical products derived from biotechnology are on the increase and the formulation of these products requires some unique skills and novel approaches. Formulation development aspects of these products are described elsewhere (see chap. 9).

## Formulation Principles

### *Influence of the Route of Administration*

Since parenteral preparations are introduced directly into the intra- or extracellular fluid compartments, the lymphatic system, or the blood, the nature of the product and the desired pharmacological action are factors determining the particular route of administration to be employed. The desired route of administration, in turn, places certain requirements and limitations on the formulations as well as the devices used for administering the dosage forms. Consequently, a variety of routes of administration (see chap. 2) are used.

One of the most important considerations in formulating a parenteral product is the appropriate volume into which the drug should be incorporated. The IV route is the only route

in which there are no strict limits of the volumes and as much as fifty milliliters can be administered by the IV route, via hypodermic injection, and several liters can be administered over the course of several hours through an IV administration system. Volumes up to 10 mL can be administered intraspinally, while the intramuscular route is normally limited to 3 mL, subcutaneous to 2 mL and intradermal to 0.2 mL.

The choice of the solvent system or vehicle is directly related to the intended route of administration of the product. IV and intraspinal injections are generally restricted to dilute aqueous solutions, whereas oily solutions, cosolvent solutions, suspensions, and emulsions can be injected intramuscularly and/or subcutaneously.

Isotonicity is another factor that must be taken into consideration. Although isotonic solutions are less irritating, cause less toxicity, and eliminate the possibility of hemolysis, it is not essential that all injections be isotonic. In fact, for subcutaneous and intramuscular injections hypertonic solutions are often used to facilitate absorption of drug because of local effusion of tissue fluids. With IV solutions, isotonicity becomes less important as long as administration is slow enough to permit dilution or adjustment in the blood. However, intraspinal injections must be isotonic because of slow circulation of the cerebrospinal fluid in which abrupt changes of osmotic pressure can give rise to severe side effects.

New routes of administration include intraarticular, directly into the synovial fluid for rheumatoid diseases and even intradigital, between the fingers, in order to better target the lymphatics. The parenteral routes of administration will influence the design of novel dosage forms and drug delivery systems especially as more potent agents from biotechnology are developed.

This chapter focuses on the physicochemical aspects of formulating a stable product in a suitable container recognizing that safety must be established through evaluation of toxicity, tissue tolerance, pyrogenicity, sterility, and tonicity, and efficacy must be demonstrated through controlled clinical investigations.

#### *Selection of Vehicle*

Most parenteral products are aqueous solutions. Chemically, the high dielectric constant (DC) of water makes it possible to dissolve ionizable electrolytes and its hydrogen-bonding potential facilitates the solution of alcohols, aldehydes, ketones, and amines. Water for injection (WFI) is the solvent of choice for making parenterals. When it is not possible to use 100% aqueous solution for physical or chemical reasons, other means of solubilization including the addition of solubilizing agents or cosolvents may be necessary. For instance, nonpolar substances (i.e., alkaloidal bases) possess limited solubility in water and it is necessary to add a cosolvent such as glycerin, ethanol, propylene glycol, or polyethylene glycol. In other cases, to prevent chemical degradation (i.e., hydrolysis, oxidation, decarboxylation, or racemization) water may have to be eliminated partially or totally. Most proteins and peptides require an aqueous environment, and the addition of salt, buffer, or other additives for solubility purposes often leads to conformational changes. Consequently, parenteral product formulators should be aware of not only the nature of the solvent and solute in parenterals but also the solvent-solute interactions and the route of administration. Typically, aqueous solution formulations are prepared by simple solution of the drug and the excipients, by *in situ* salt formation of the drug in the solution (titrating against an acid or base), or by complexation of the drug with a complexing agent.

**Solubility and solubilization.** The solubility of a substance at a given temperature is defined quantitatively as the concentration of the dissolved solute in a saturated solution (i.e., the dissolved solute phase). Generally, drugs are present in solution at unsaturated or subsaturated concentrations; otherwise, crystallization of the drug may occur as a result of changes in pH, temperature, by seeding from other ingredients, or particulates in the solution.

The solubilization techniques for injectable formulations include pH adjustment, mixed aqueous/organic cosolvents, oily vehicles, surface-active agents, complexation, as well as formulating the drug in emulsion, suspension, liposomes, nanosuspensions, and combinations of techniques. An excellent review of the solubilizing excipients that could be used in the injectable formulations has been provided by Strickly (2).

**Table 1** Expressions for Approximate Solubility

| Term                               | Relative amount of solvent to dissolve |
|------------------------------------|----------------------------------------|
| Very soluble                       | <1                                     |
| Freely soluble                     | 1–10                                   |
| Soluble                            | 10–30                                  |
| Sparingly soluble                  | 30–100                                 |
| Slightly soluble                   | 100–1,000                              |
| Very slightly soluble              | 1,000–10,000                           |
| Practically insoluble or insoluble | >10,000                                |

**Table 2** Typical Examples of Drugs Representing the Solubility Terms

| Term                               | Drug            | Solubility of drug |
|------------------------------------|-----------------|--------------------|
| Very soluble                       | Chloral hydrate | >8 g/mL            |
| Freely soluble                     | Isoniazid       | 0.330 g/mL         |
| Soluble                            | Guaifensin      | 0.050 g/mL         |
| Sparingly soluble                  | Pyrazinamide    | 0.015 g/mL         |
| Slightly soluble                   | Salicylic acid  | 0.002 g/mL         |
| Very slightly soluble              | Griseofulvin    | 0.000,02 g/mL      |
| Practically insoluble or insoluble | Diclofenec      | 0.000,002 g/mL     |

Source: Adapted from Ref. 3.

**Solubility expressions.** Solubility of a substance can be expressed in a number of ways. Generally, the concentration is expressed as percent (w/v), that is, grams per 100 mL of solution, but molarity and molality have been used. Molarity is defined as the number of moles per 1000 mL of solution. Molality is the number of moles of solute per 1000 g of solvent and, therefore, being a weight relationship, is not influenced by temperature. The USP lists solubility in terms of the number of milliliters of solvent required to dissolve 1 g of substance. If exact solubilities are not known, the USP provides general terms to describe a given range. These descriptive terms are listed in Table 1. Typical examples of drugs representing the solubility terms are listed in Table 2 (3).

**Bonding forces.** For a substance to dissolve, the forces of attraction that hold the molecules together must be overcome by the solvent. The solubility will be determined by the relative binding forces within the substance (solute-solute interactions) and between the substance and the vehicle (solute-solvent interactions). If an environment similar to that of the crystal structure can be provided by the solvent, then the greater the solubility (i.e., "like dissolves like"). Ionic compounds dissolve more readily in water by virtue of ion-dipole interactions, whereas hydrophobic substances dissolve more easily in organic solvents as a result of dipole or induced dipole interactions.

Often, the solubility of the drug substance is due in large part to the polarity of the solvent, generally expressed in terms of dipole moment, which is related to the DC. Solvents with high DCs dissolve ionic compounds and are water soluble, whereas solvents with low DCs are not water soluble and do not dissolve ionic compounds. The former are classified as polar solvents (e.g., water, glycerin, and ethanol), while the latter are nonpolar (e.g., chloroform, benzene, and the oils). Solvents with intermediate DCs (e.g., acetone and butanol) are classified as semipolar. The DCs of most pharmaceutical solvents are known (4) and values for a number of binary and tertiary blends have been reported (5) and, if not reported, can be readily estimated (6,7). Table 3 is a listing of the DCs of some solvents at 25°C.

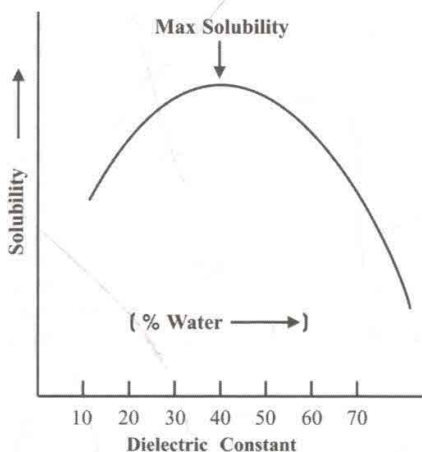
The solubility profiles of a number of pharmaceuticals as a function of DC have been reported by Paruta and coworkers (8–10). By determining the solubility of a substance in a system at various DCs, a graph such as that shown in Figure 1 can be constructed to determine the DC that will provide the required solubility for a particular drug substance. As can be seen

**Table 3** DCs of Some Solvents at 25°C

| Solvent                                                | DC          |
|--------------------------------------------------------|-------------|
| Water <sup>a</sup>                                     | 78.5        |
| Glycerin <sup>a</sup>                                  | 40.1        |
| <i>N,N</i> -dimethyl acetamide <sup>a</sup>            | 37.8        |
| Propylene glycol <sup>a</sup>                          | 32.0 (30°C) |
| Methanol                                               | 31.5        |
| Cremophor EL (R) (polyoxyl castor oil 35) <sup>a</sup> | 27.0        |
| Ethanol <sup>a</sup>                                   | 24.3        |
| <i>N</i> -propanol                                     | 20.1        |
| Acetone                                                | 19.1        |
| Benzyl alcohol <sup>a</sup>                            | 13.1        |
| Polyethylene glycol 400 <sup>a</sup>                   | 12.5        |
| Cottonseed oil <sup>a</sup>                            | 3.0         |
| Benzene                                                | 2.3         |
| Dioxane                                                | 2.2         |

<sup>a</sup>Solvents used in parenterals

Abbreviation: DC, dielectric constant.

**Figure 1** Hypothetical plot of solubility of a substance versus dielectric constant in various mixtures of dioxane and water.

from the plot, to obtain the maximum concentration, a DC of around 40 is required. Not all mixtures will show a maximum, but such a plot illustrates the required DC to obtain the desired concentration. For example, if a DC (DC) of 60 was selected, a mixture of water (DC = 78.5), polyethylene glycol (PEG) 400 (DC = 12.5) and ethanol (DC = 24.3) could be used. Selecting an amount of ethanol necessary to dissolve the drug (e.g., 10%), the percentages of PEG 400 and water can be calculated as follows:

$$(10)(24.3) + (X)(78.5) + (90 - X)(12.5) = (100)(60)$$

where X is the percentage of water required and is calculated to be 73.5%.

Therefore, the vehicle to provide a DC of 60 will have the following composition: Ethanol 10%, PEG 400 16.5%, and Water 73.5%

Since DC is a measure of the polarizability and dipole moment of a compound, several researchers have explored other parameters and polarity indices (11) which include molecular volume, solvent and solute interactions and specific interactions such as hydrogen bonding. In 1952, Hildebrand and Scott (12) introduced solubility parameters to predict solubility of regular solutions. Since pharmaceutical systems deviate from regular or ideal solutions, Martin and coworkers (13) modified the Hildebrand approach to include hydrogen-bonding and

dipolar interactions. The molecular surface area of the solute and interfacial tension between solute and solvent were further used by Amidon (14) and Yalkowsky (15) to predict solubility. Among the many theoretical models available to predict solubility in water, recent reports review the available models and discuss the potential and limitations of these computational approaches (16,17).

Hydrogen bonding, a type of dipole-dipole interaction, is an important determinant of solubility. Because of its small size, the hydrogen atom (proton donor) with its positive center, can approach the negative center (electron donor) of a neighboring dipole more closely than any other atom. As a result of this spatial maneuverability, both intramolecular bonding (i.e., between groups within a single molecule) and the intermolecular type (i.e., among molecules) can occur. The latter is responsible for association in most solvents and dissolution of most drugs. Alcohols dissolve in water by hydrogen bonding, up to an alkyl chain length of five carbon atoms. Phenols dissolve in water and alcohol and, as the number of hydroxyl groups increase, the water solubility is enhanced because of the increased opportunity for hydrogen bonding. Most aromatic carboxylic acids, steroids, and cardiac glycosides are not water soluble but dissolve in alcohol, glycerin, or glycols by hydrogen bonding.

Dipole-ion interaction is another important molecular property that is responsible for the dissolution of ionic crystalline substances in polar solvents (i.e., water or alcohol). Ions in aqueous solution are generally hydrated (surrounded by water molecules) by as many water molecules as can spatially fit around the ion. The attributes of a good solvent for electrolytes include: (i) a high-dipole moment; (ii) a small molecular size; and (iii) a high DC to reduce the force of attraction between the oppositely charged ions in the crystal. Water possesses all of these characteristics and is, therefore, a good solvent for electrolytes. The cation of the electrolyte is attracted to the negative oxygen atom, while the anion attracts the hydrogen atoms of the dipolar water molecules.

Symmetrical molecules, such as benzene and carbon tetrachloride, possess zero dipole moment and are nonpolar. Solubility of such molecules or their existence in a liquid state is due to van der Waals forces. Other intermolecular interactions, such as London forces or Debye interactions are also responsible for solubility of such nonpolar substances.

**Effect of temperature.** Substances generally dissolve faster if heat is applied to the system and the solubility of most solids is increased by an increase in temperature. This is true if the substance absorbs heat during the course of dissolution. The degree to which temperature can influence solubility is determined by the heat of solution, more specifically the differential heat of solution,  $\Delta H$ , which represents the rate of change of the heat of solution per mole of solute in a solution of specified concentration. The higher the heat of solution, the greater is the influence of temperature on solubility.

The following equation shows the influence of temperature on solubility:

$$\frac{d \ln S}{dT} = \frac{\Delta H}{RT^2} \quad (1)$$

where  $S$  is the solubility or concentration of a saturated solution, often expressed in terms of molality, molarity, or mole fraction;  $R$  is the gas constant; and  $T$  is the absolute temperature. Equation (1) can be written as

$$\log S = \frac{\Delta H}{2.303R} \times \frac{1}{T} + \text{constant} \quad (2)$$

By plotting the logarithm of the solubility in moles per liter versus the reciprocal of the absolute temperature as shown in Figure 2, the differential heat of solution can be calculated from the slope of the line, which is equal to

$$-\frac{\Delta H}{(2.303)(1.987)}$$

A positive heat of solution indicates that the process is endothermic (i.e., the solute absorbs heat when dissolving). Therefore, an increase in temperature will increase solubility. A

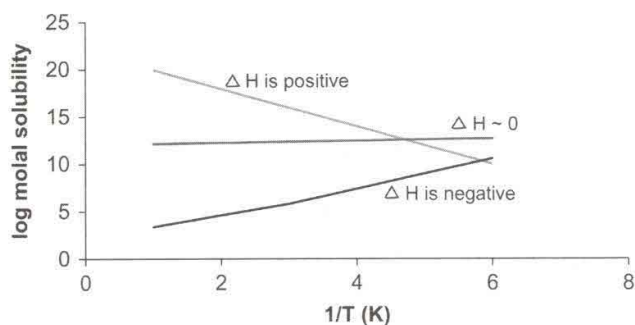


**Figure 2** Effect of temperature on solubility of a substance.  $\Delta H$  represents the differential heat of solution and is calculated from the slope of the line,  $-\frac{\Delta H}{(2.303)(1.987)}$ .

negative value indicates that the process is exothermic (i.e., the solute evolves heat when dissolving). In this case, increase in temperature results in a decrease in solubility. A differential heat of solution around zero indicates that the solubility is not significantly influenced by temperature.

**Measuring solubility.** Methods for determining the solubility of drug substances in aqueous solvents have been described (18,19). The standard way to determine the solubility of a compound is to use the "shake-flask" solubility method. This method is inherently low-throughput, labor intensive, and necessitates the addition of drug in a powder form. It involves adding an excess quantity of solid material to a volume of buffer at a fixed pH and the saturated solution is agitated (shake-flask) until equilibrium is reached, generally 12 hours to seven days. Following separation by filtration or centrifugation, the compound in solution is analyzed and quantified by a suitable analytical technique such as UV/Vis spectroscopy or high-performance liquid chromatography (HPLC). The other classical experimental methods used to determine solubility are turbidimetric ranking assays, HPLC-based assays, and potentiometric methods. The newer high-throughput methods which determine both kinetic and thermodynamic (equilibrium) solubilities are based on screening multiple solutes and solvents, in array of compositions, using 96-well format that allows for solubility analysis in a single plate with very low drug amount (19,20).

**Solubilization techniques.** A variety of approaches to increase the aqueous solubility of an otherwise less soluble or insoluble drug substance to a desired level for optimum injectable product have been reported and reviewed (2,21,22). These include: 1) pH adjustment, 2) salt formation, 3) use of cosolvents, 4) surfactants as solubilizers, 5) use of complexing agents, and others. Metabolizable oils as vehicles have also been used for certain class of compounds. Beyond these solubilization approaches, it may become necessary in some cases to change the formulation from solution to dispersed system such as emulsion, suspension, and more recently liposomes and nanosuspensions.

**pH adjustment** Most organic drug substances are weak electrolytes and, therefore, exist in solution in dissociated and undissociated forms. The ratio of these forms is determined by the pH of the solution as per the Henderson-Hasselbach relationship. As a result, properties such as solubility, partition coefficient, and chemical stability, which are markedly different for the undissociated and dissociated forms are influenced by pH.

Many of the organic electrolytes used in parenteral systems contain a basic nitrogen atom in the molecules. These include antihistamines, alkaloids, local anesthetics, and so on, which are practically insoluble in water but dissolve readily in dilute solutions of acids because of salt formation. The addition of alkali to these solutions increases the pH and causes free base to precipitate. Examples are atropine sulfate, ephedrine sulfate, lidocaine hydrochloride, and pyribenzamine hydrochloride.

In compounds that contain an electron withdrawing group, such as oxygen, a positive center is created, which in turn attracts electrons from adjacent nitrogen, and if a hydrogen

atom is attached, the N-H bond is weakened. As a result, in alkaline solution a more soluble anion is formed. The examples are phenobarbital and sulfanilamide.

The addition of acid to the solutions of these compounds will cause the free acid form to precipitate. Even the addition of a salt of a strong acid such as morphine sulfate will result in precipitation.

Most marketed injection products are in the pH range of 4 to 8 for biocompatibility reason, however, some are outside of this range. The pH solubility and pH stability-rate profiles of a drug usually determines the pH at which a product is formulated (23). Additional formulation variables to be considered are the necessity of a buffer, buffer capacity, and drug concentration. These variables are described in details in a further section (see "Added Substances").

**Salt formation** Salts of acidic and basic drugs usually exhibit higher solubility than their corresponding acid or base forms. Therefore, salt formation is the most preferred and effective method of increasing solubility and dissolution rates of acidic and basic drugs (24,25).

Solubility-pH profiles of weakly acidic or basic organic drugs may be visualized on the basis of classical Henderson-Hasselbach relationship. In the case of monoprotic acid, a saturated solution can be defined by the following equations and corresponding constants (26).

$$HA \rightleftharpoons H^+ + A^- K_a = \frac{[H^+][A^-]}{[HA]} \quad (3)$$

$$HA(\text{Solid}) \rightleftharpoons HA(\text{Solution}) S_0 = [HA] \quad (4)$$

where [HA] is the concentration of undissociated acid form,  $[A^-]$  is the concentration of corresponding salt form,  $[H^+]$  is the concentration of proton or dissociated hydrogen, and  $S_0$  is the intrinsic solubility of the monoprotic acid. Solubility,  $S$ , at a particular pH is defined then as mass balance sum of the concentrations of all of the species dissolved in the aqueous phase.

$$S = [A^-] + [HA] \quad (5)$$

Rearranging equations (3), (4), and (5),

$$\begin{aligned} S &= K_a [HA] / [H^+] + [HA] \\ &= S_0 (K_a / [H^+] + 1) \\ &= S_0 (10^{-pK_a + pH} + 1), \text{ or} \\ \log S &= \log S_0 + \log (10^{-pK_a + pH} + 1) \end{aligned} \quad (6)$$

For a weakly acidic drug, depending on the pH of the solution, the term,  $\log (10^{-pK_a + pH} + 1)$ , changes solubility function according to the conditions below.

1.  $pH \gg pK_a$

The exponent  $(-pK_a + pH)$  remains positive and very large number compared with 1, and hence, 1 is ignored, and

$$\begin{aligned} \log (10^{-pK_a + pH} + 1) &\text{ becomes } \log (10^{-pK_a + pH}) \text{ or} \\ &(-pK_a + pH) \log (10) \text{ or } (-pK_a + pH) \\ \text{Therefore,} \\ \log S &= \log S_0 - pK_a + pH \\ \text{Since } pK_a &\text{ is a constant.} \\ \log S &= (\log S_0 - pK_a) + pH \end{aligned} \quad (7)$$

Equation (7) is of the form,  $Y = c + mX$  or an equation of a straight line with associated intercept and slope,  $c$  and  $m$ , respectively.

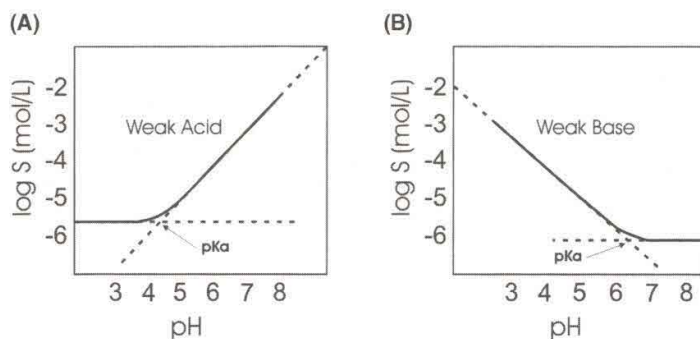


**Figure 3** Solubility/pH profile for weak acid ( $pK_a = 4.4$ ) and weak base ( $pK_a = 6.1$ ). Source: Adapted from Ref. 26.

Therefore, a plot of  $\log S$  versus pH, will yield a straight line the slope of which will be equal to +1 and the intercept will be  $(\log S_0 - pK_a)$ . A similar relationship can be made for a weakly basic drug, in which case, the slope will be equal to -1.

Figure 3 (26) shows the solubility-pH profile for a (i) weak acid ( $pK_a$  4.4,  $\log S_0$  -5.6) and (ii) weak base ( $pK_a$  6.1,  $\log S_0$  -5.9).

2.  $pH = pK_a$ , or at the inflection point in the curve.

The exponent  $(-pK_a + pH)$  becomes zero and the term

$$\log(10^{-pK_a + pH} + 1) \text{ becomes } \log(10^0 + 1) \text{ or } \log(1 + 1).$$

Therefore,

$$\log S = \log S_0 + 0.3$$

3.  $pH \ll pK_a$ , or at the flat line of the curve.

The exponent  $(-pK_a + pH)$  remains negative.

$$\log(10^{-pK_a + pH} + 1) \text{ becomes } \log(0.000\dots + 1) \text{ or close to } 0.$$

Therefore,

$$\log S \cong \log S_0$$

Whether certain acidic or basic drugs would form salts and, if salts are formed, dissociation back to the free acid or base forms would depend on several factors, such as pH,  $pK_a$ ,  $S_0$  (intrinsic solubility),  $k_{sp}$  (solubility product) and  $pH_{max}$  (pH of maximum solubility). The aqueous solubility of an acidic or basic drug as a function of pH determines if the compound will form suitable salts within the physiologically acceptable pH range. Moreover, the common-ion effect of the salt-forming agents is also important in determining the final solubility. It has been reported that dissolution rates of a hydrochloride salt decrease as the pH of an aqueous medium is lowered when HCl is added or if NaCl is added to the medium. Similarly, the dissolution rate of a sodium salt decreases in the presence of added NaCl in the medium. There are numerous reports in the literature indicating such common-ion effects on salts having relatively low aqueous solubilities (27).

A review by Serajuddin about the principles of salt formation and its utility in formulation has recently been published (28). It surveyed about 120 salts approved by the FDA during the 12-year period from 1995 to 2006 and showed that the hydrochloride salt was the predominant salt form among the basic drugs and the sodium salt was the predominant form for acidic drugs. About 77% of the salts of basic drugs were prepared with relatively stronger counterions (hydrochloride, hydrobromide/bromide, sulfate/bisulfate and nitrate). Similarly, 14 out of 19 salts of acidic drugs were prepared with strong alkalies such as NaOH and KOH.

**Use of cosolvents** If the pH adjustment or salt formation approach still results in aqueous solubility of a drug well below its therapeutic dose, a mixture of solvents may be used to achieve sufficiently high solubility. A cosolvent is a water-miscible organic solvent that is used to increase the solubility of a poorly water-soluble compound. The addition of cosolvent results in reduction of polarity of water which in effect reduces the surface tension, DC, and solubility parameter of water. The increase in solubility by cosolvents is much more dramatic for nonpolar solutes (can be several orders of magnitude), than for solutes of intermediate polarity. Another advantage of using cosolvents is that a change in solvent property may help considerably in stability for drugs which may exhibit hydrolytic degradation by reducing the concentration of water in the formulation. Cosolvent may also enhance the stability of a drug by providing a less suitable environment for the transition state of the reactants, provided the transition state is more polar than the reactants. It is reported that cosolvents are employed in approximately 10% of the FDA approved injectable products (22).

**Cosolvents and solubility** J. H. Hildebrand, in a series of papers published beginning in 1916, described the basic principles of solutions and solubility and introduced the cosolvency approach (29) and experimental tests of a general equation for solubility (30). Since then, numerous theoretical cosolvency models have been proposed that correlate and/or predict the solubility of drugs in water cosolvent mixtures (31–34) and have been reviewed extensively by Jouban (35). The simplest experimental cosolvency model, that is, the log-linear model of Yalkowsky (36–38), provides an estimate of drug solubility in water-cosolvent mixtures using aqueous solubility of the drug. It is expressed as:

$$\log S_m = f \log S_c + (1 - f) \log S_w \quad (8)$$

Where  $S_m$  is the solute's solubility in water-cosolvent mixture,  $f$  is the volume fraction of cosolvent,  $S_c$  is the solubility of drug in pure cosolvent, and  $S_w$  is the solubility of drug in water.  $S_x$  values can be expressed in g/L, mole fraction, etc. Equation (8) can be further simplified as

$$\log S_m = \log S_w + f\sigma \quad (9)$$

where

$$\sigma = \log ac_w - \log ac_c \quad (10)$$

And  $ac_w$  and  $ac_c$  are the activity coefficients for the drug in water and cosolvent, respectively. In a given cosolvent system,  $\sigma$  will be constant. Therefore, if one plots  $\log S_m$  versus  $f$ , the slope will be  $\sigma$ . Comparing slopes of different cosolvent-water systems can easily be done by using  $\sigma$  as a measure of the solubilization potential of the cosolvent. In practice, experimental methods of characterizing the solubility of cosolvent systems can be utilized with the aid of statistical experimental design. Advantage of the experimental approach is that one can use additional excipients, for example, surfactants, buffers, etc., in screening experimental designs.

**Cosolvents and stability** Cosolvents cannot only increase the solubility of drugs but may also increase the stability of some drugs (31). The addition of cosolvent reduces the collision probability between a water molecule and a drug molecule which is necessary for hydrolysis. As mentioned earlier, the degradation rate of a drug may change with the DC of the medium. Decreasing the polarity of the reaction medium by the addition of cosolvent unfavors the formation of the charged species. It stabilizes a solute against any reaction that produces charged products or proceeds through a charged transition state (39,40). As a general rule, for reactions leading to products that are less polar than the starting material, a less polar medium may accelerate the reaction. On the other hand, reactions leading to products that are more polar than the starting material may proceed rapidly in polar media.

Improvement of stability of a drug in the presence of cosolvent was reported by Ni, et al (41). The authors studied the stability of an anticancer compound, SarCNU (a nitrosourea derivative), in several pharmaceutically acceptable solvents such as water, EtOH, propylene

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.

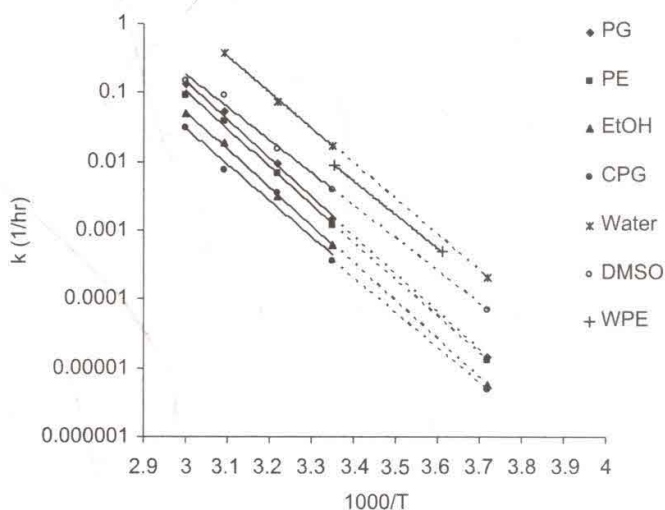


**Figure 4** Stability behavior of SarCNU in the presence of various cosolvent.

**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%<br>Ethyl alcohol 10%                              |
| Digoxin          | Lanoxin    | Propylene glycol 40%<br>Ethyl alcohol 10%                              |
| Melphalan        | Alkeran    | Propylene glycol 60%<br>Ethyl alcohol 5%                               |
| Methocarbamol    | Robaxin    | Polyethylene glycol 50%                                                |
| Oxytetracycline  | Terramycin | Propylene glycol 67–75%                                                |
| Paricalcitol     | Zemlar     | Propylene glycol 30%<br>Ethyl alcohol 20%                              |
| Phenobarbital Na | Nembutal   | Propylene glycol 40%<br>Ethyl alcohol 10%                              |
| Phenytoin Na     | Dilantin   | Propylene glycol 40%<br>Ethyl alcohol 10%                              |
| Teniposide       | Vumon      | <i>N,N</i> -dimethylacetamide 6%<br>Cremophor 50%<br>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).

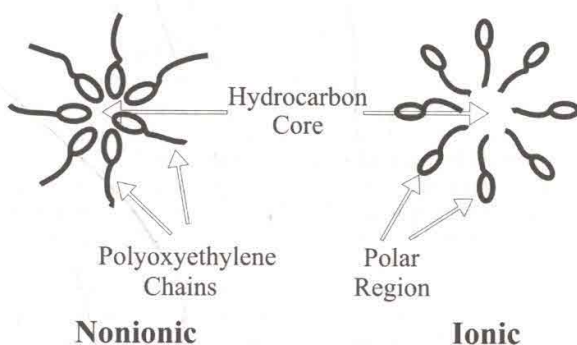


**Figure 5** Illustration of spherical orientations of nonionic and ionic micelles.

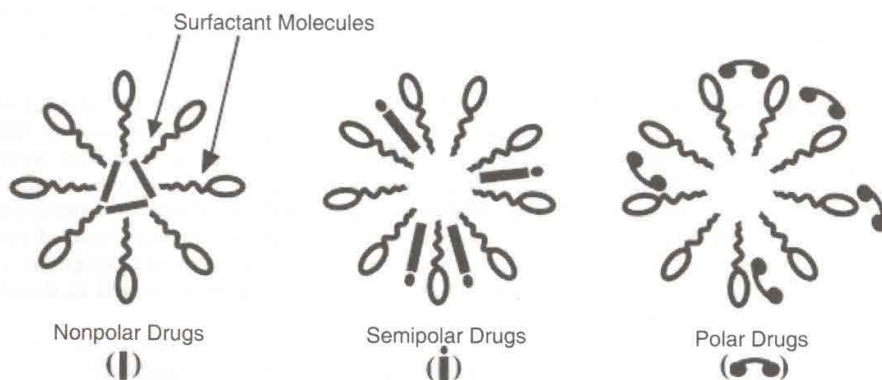


**Figure 6** Schematic representation of mechanisms of micellar solubilization.

**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

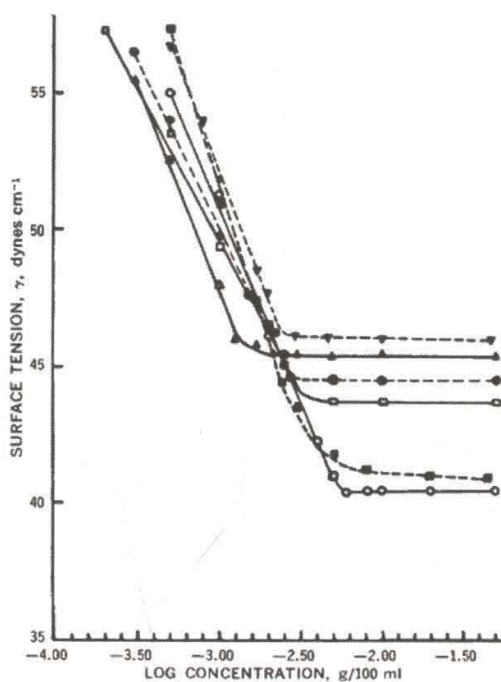


**Figure 7** Surface tension versus concentration of surfactant. Break in the curve denotes CMC. Source: From Ref. 50.

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 (LD<sub>50</sub>, 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<br>Tenoposide/vumon/55<br>Cyclosporine/sandimmune/65            |
| Solutol HS   | Polyethylene glycol 660 hydroxystearate | 14–16                  | 0.03        | Vitamin K /Aqua-mephyton/25                                                           |
| Pluronic-F68 | Polaxomer                               | >24                    | 0.1         | Recombinant Growth hormone/accretropin/0.2                                            |
| Polysorbates | Tween-80                                | 15                     | 0.0014      | Amiodorone/cordarone/10<br>docetaxel/taxotere/100<br>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 amphipathic (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

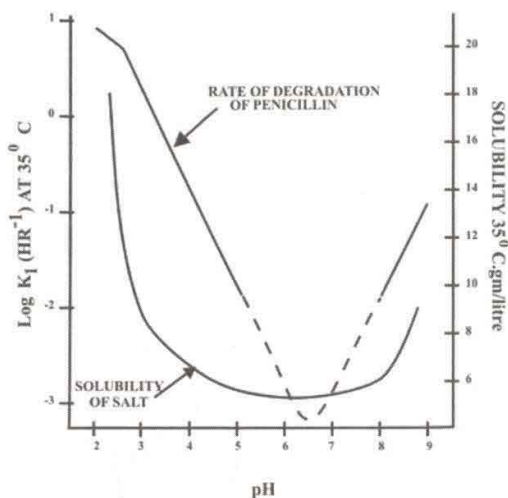


**Figure 8** Solubility/stability pH profile of procaine penicillin. Source: From Ref. 77.

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:

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

where

$dB$  = change in concentration of base or acid,  
 $dpH$  = change in pH,  
 $C$  = molar concentration of buffer system, and  
 $K_a$  = dissociation constant of the buffer.

A hypothetical plot of  $\beta$  versus pH- $pK_a$  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  $pK_a$  of the buffer system and further suggests that a buffer system with a  $pK_a$  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  $pK_a$  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.

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

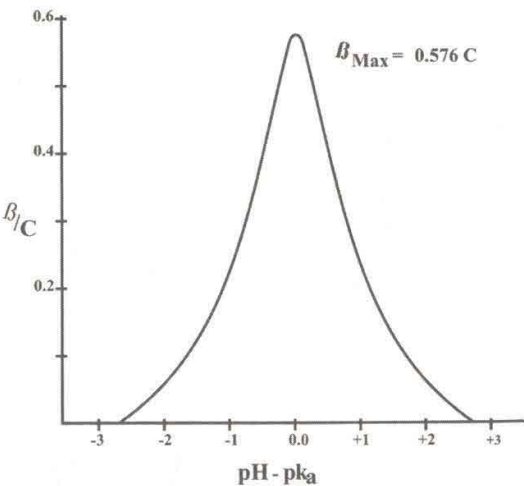


Figure 9 Theoretical buffer capacity curves of a monobasic acid.

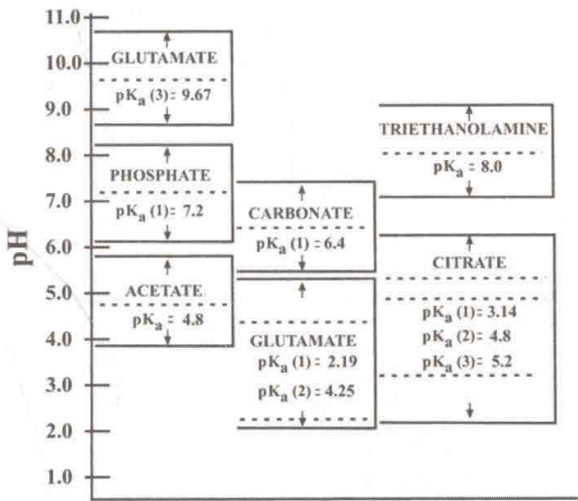


Figure 10 Effective range of pharmaceutical buffers, indicated by the arrows. The dashed line represents the  $pK_a$  value.

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.

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

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

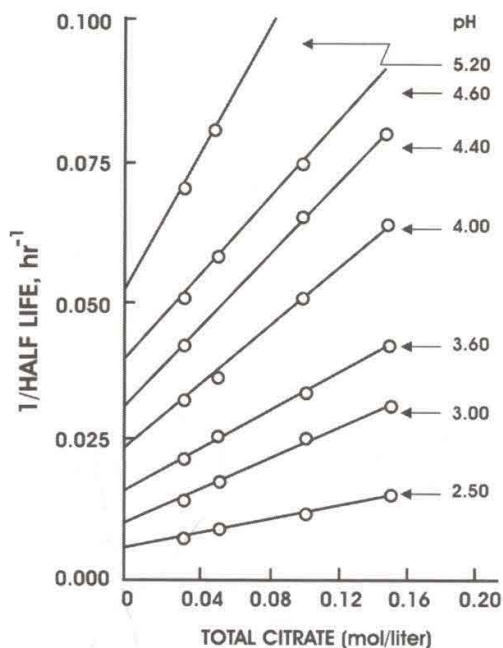


**Figure 11** Effect of citrate buffer concentration on thiamine hydrolysis (vitamin B1) at 96.4°C at constant ionic strength and at different pH values. Source: From Ref. 78.

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

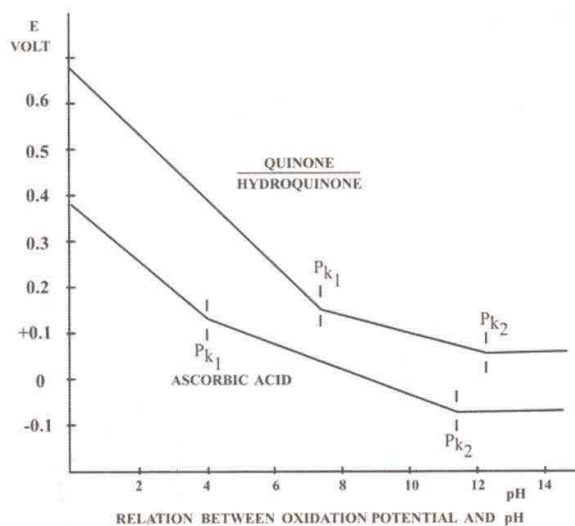


**Figure 12** Relationship between oxidation potential and pH. Source: From Ref. 81.

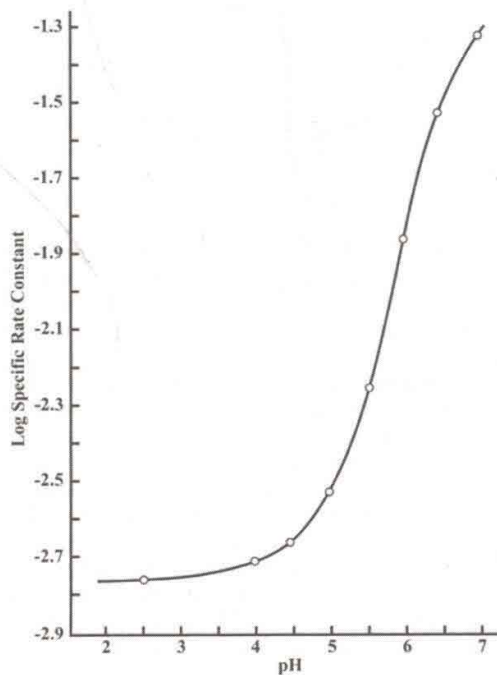


**Figure 13** Reaction rate constant for the first-order oxidative degradation of morphine at 95°C as a function of pH. Source: From Ref. 82.

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                         | $E^a$ (V) | pH   | Temperature ( $^{\circ}\text{C}$ ) |
|-----------------------------------|-----------|------|------------------------------------|
| 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<br>0.005–0.03 others | 0.18<br>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:

$$E = 17 \frac{L_{iso}}{M} \tag{14}$$

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  |
| Unitrivalent 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<br>mean mOsm $\pm$ SD | Sodium chloride equivalent method |                       |
|----------------------------------------|-------------------------------------------|-----------------------------------|-----------------------|
|                                        |                                           | Osmolality                        | Percent of<br>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,

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

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  $0.90$  g -  $0.48$  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/<br>Decadron <sup>®</sup><br>(8 mg/mL) | Medroxyprogesterone<br>Acetate/Depo-Provera <sup>®</sup><br>(100 and 400 mg/mL) | Triamcinolone<br>Acetonide/Kenalog <sup>®</sup><br>(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

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|                                         |
|-----------------------------------------|
| 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                          |

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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 homogenous mixture is formed. The oil phase is then added with stirring or shaking to form a “premix” with large (>10  $\mu\text{m}$ ) droplets, which is then subjected to a high-energy mechanical homogenization. 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  $\mu\text{m}$  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, osmolality, 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  $\mu\text{m}$  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  $\mu\text{m}$  (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 - dimyristoylphosphatidylcholine 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  $\mu$ 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.

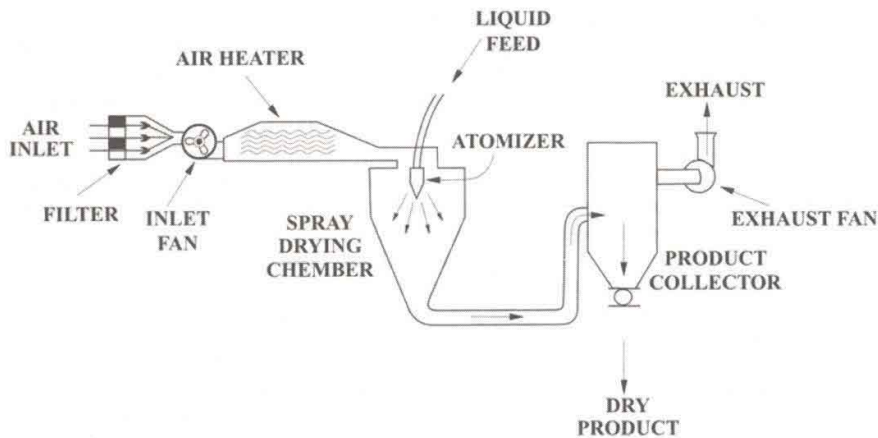


**Figure 14** Schematic representation of spray-drying process.

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 |
|--------------------------|---------------|---------------------|-----------------------|
| Actreonam/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/Ixemptra     | 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  $2^\circ\text{C}$  higher than  $T_g'$ , which is often associated with the glass transition temperature in the frozen state (133).  $T_c$  equals the eutectic temperature ( $T_{eu}$ ) 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

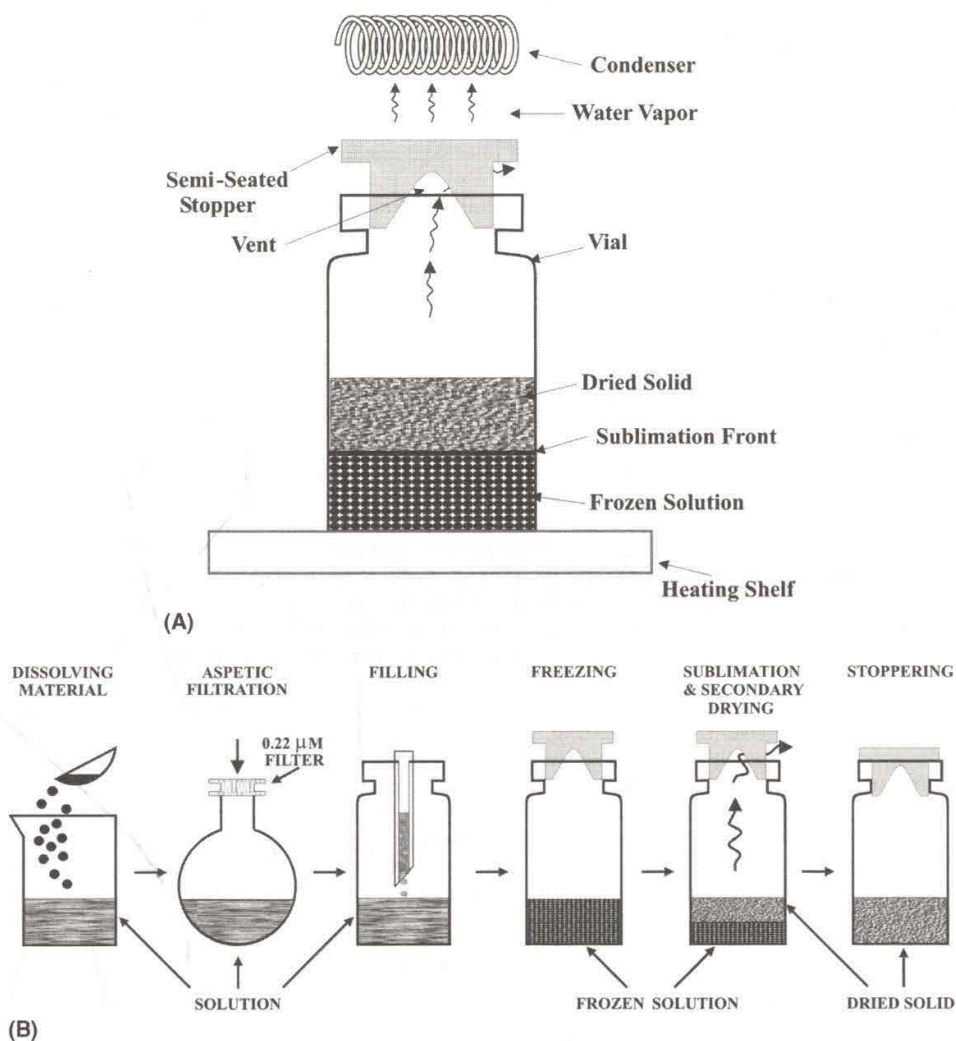


**Figure 15** Schematic representation of freeze-drying process.

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

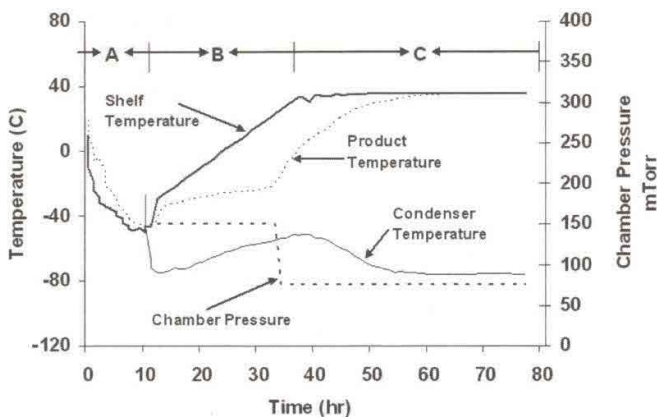


Figure 16 Typical product temperature/chamber pressure curve during freeze-drying.

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

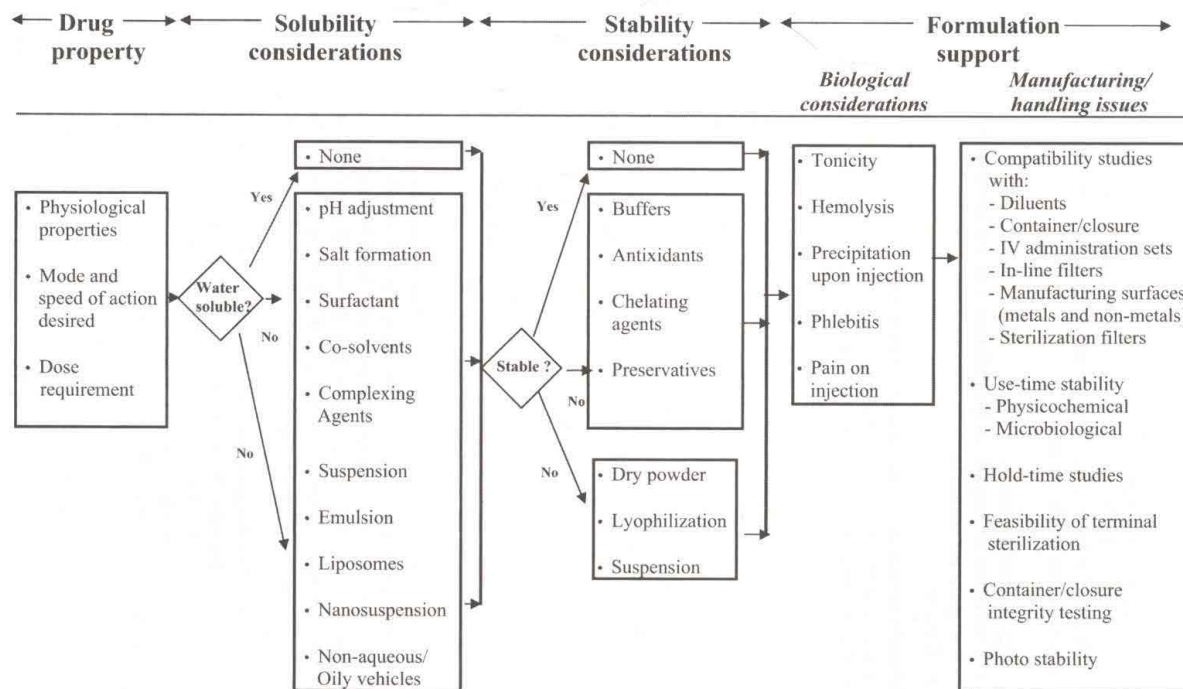
Temperature and pressure curves for a typical cycle are illustrated in Figure 16 for Mannitol solution (5% w/w) filled into 10 mL glass vial (5 mL/Vial). Freezing stage is denoted by "A," primary drying by "B," and secondary drying by "C." During freezing as the shelf temperature is lowered the product 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

**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)       |
| Cations                                      |               |              |               |
| 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           |
| Anions                                       |               |              |               |
| 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 <sup>-</sup>     | 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                                | 10% soybean oil                               |
| Electrolytes              | and electrolytes (Na <sup>+</sup> , K <sup>+</sup> , Cl <sup>-</sup> acetate, and phosphate) | 1.2% egg yolk phospholipids<br>2.25% glycerin |
| Antioxidant               | May be present                                                                               | —                                             |
| Buffering capacity        | Moderate                                                                                     | No                                            |
| Light Protection          | Yes                                                                                          | Low                                           |
| Container                 | Glass, plastic                                                                               | Yes                                           |
|                           |                                                                                              | 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

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>, NephrAmine<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.

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# 12 | Plastic packaging for parenteral drug delivery

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## INTRODUCTION

Driven by the development of biotechnology products, newer drug therapies, and reformulation of poorly soluble drugs, parenteral delivery is expected to provide strong growth in years to come. Routes of administration include subcutaneous, intramuscular, intradermal and intravenous injections. Drug products have been almost exclusively dispensed in glass containers, primarily because of the clarity, inertness, barrier property and thermal resistance of these containers. With the development of plastic polymer technology over the last 30 years, plastics have become logical alternatives for small-volume parenteral (SVP) and large-volume parenteral (LVP) packaging. Although plastic containers have become well-established as containers for LVP products, plastics have been, until recently, used on a limited scale for SVPs.

Glass vials are the primary container of choice because of their excellent gas and moisture barrier properties. More importantly, there is an extensive knowledge base on processing, filling, regulatory review and commercial availability of glass containers. Glass, however, may not be the best solution for all chemical or biological drug candidates. Glass contains free alkali oxides and traces of metals. Depending on the characteristics of the drug being packaged, it is likely that delamination could occur for high pH products over time, thereby affecting the shelf-life of the drug product. Proteins and peptides can be readily adsorbed onto the glass surface and can be denatured or become unavailable for treatment. With a glass prefillable syringe (PFS), potential leachables such as silicone, tungsten and adhesive can affect the stability of biopharmaceutical products. Glass may break during processing or transportation and when stored at low frozen temperatures. In these and other areas, plastic containers have made clear in-roads in the parenteral drug delivery market.

With the proliferation of new polymers and newer process technologies, most of the less-desirable characteristics of plastic containers have been overcome and the use of plastic packaging as vials and syringes is increasing. This chapter will discuss the role of plastic in pharmaceutical parenteral drug delivery. The discussion will provide insights on the following areas:

- Advances in plastic resins for SVP packaging with an emphasis on cyclic olefins as well as other plastics used: The properties of these plastics, applications and challenges will also be discussed.
- Plastic vial systems: This section will discuss in detail the development activities in this area including the use of plastic vials in lyophilization and the use of reconstitution devices.
- Plastic PFS systems: As more biopharmaceutical drugs and higher viscosity formulations are delivered in a PFS, there is the need for a break-resistant, high-quality, plastic PFS. Challenges with glass include breakage, reactivity of glass and leachables, such as silicone, tungsten and adhesive. Discussion will include how plastic PFS offer options to solve these challenges.
- IV bags and disposable bags: Following a brief overview of use of plastics for IV bags for LVPs, discussion will focus on new developments in the use of plastics for disposable bags in the packaging of biologics, including considerations for selection of disposable bags.
- Quality and regulatory considerations: U.S. Pharmacopeia (USP), European Pharmacopoeia (Ph.Eur.) and Japanese Pharmacopoeia (JP) compendial requirements will be discussed and referenced for plastic containers.

This chapter provides the reader with adequate information on recent developments, availability and use of various plastic packaging systems for pharmaceutical drug products, including suitable references to commercialized drugs products.

### ADVANCES IN PLASTICS

Plastic resins are the most widely used raw materials in global pharmaceutical packaging, accounting for 61% of consumption compared with glass, paper products and aluminum foil. The worldwide demand for plastics for packaging was estimated at \$25.8 billion or 2.3 billion lbs. of material consumed in 2006 (1). High-density polyethylene (PE) is the most widely used plastic with 1.2 billion lbs. consumed, followed by polypropylene (PP) at 0.4 billion lbs. However, the fastest growth is expected with the newer resins, the cyclic olefins growing at a compound annual growth rate of 5.5% by 2011 (Fig. 1). The growth is expected to penetrate specialty fields such as pharmaceutical drug delivery. This is driven by a need for clear, highly transparent, biocompatible packaging systems with improved quality and improved barrier protection.

*Cyclic olefins:* Compared with the traditional plastic resins, the development and application of cyclic olefins in parenteral drug delivery is relatively new. Cyclic olefins are prepared by additional polymerization of monocyclic olefins, cyclobutane or cyclopentane or bicyclic olefins such as norbornene. The resulting product has improved chemical and physical properties, such as glass-like transparency, excellent chemical resistance and improved moisture barrier. Mitsui Petrochemical Industries produced copolymers of ethylene and other cyclic olefins. Starting in the 1980s, Mitsui and Hoechst (2,3) began using single-sited metallocene catalysis in the polymerization of cyclic olefins that led to the development of the cyclic olefin copolymer (COC) Topas<sup>®</sup> by Ticona. In this process, 2-norbornene was reacted with ethylene in the presence of a metallocene catalyst to produce a series of copolymers whose properties can be modified by varying the norbornene percentage in the material. Another commercially viable route is through a two-step process based on the ring-opening metathesis polymerization (ROMP) of dicyclopentadiene followed by complete hydrogenation of the double bonds to form cyclic olefin polymers (COP) (Fig. 2). Using this process, the Zeon Corporation developed the Zeonex<sup>®</sup> and Zeonor<sup>®</sup> line of COP. A similar process also resulted in another clear COP plastic, called Daikyo Crystal Zenith<sup>®</sup> (CZ) that is available only in a finished container format from Daikyo Seiko, Ltd.

COP and copolymers (COC) possess many excellent properties, including glass-like transparency. This glass-like transparency of the polymers permits visual inspection of

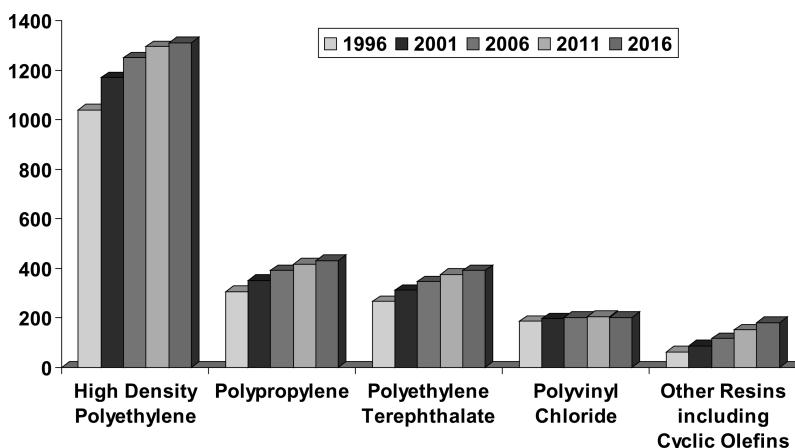


Figure 1 (See color insert) World pharmaceutical packaging plastics demand by resin (million pounds by weight).

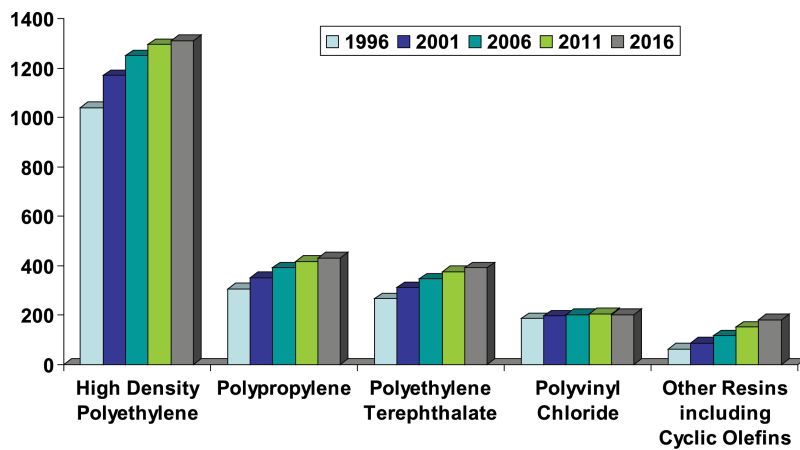


**Figure 12.1** World pharmaceutical packaging plastics demand by resin (million pounds) (*see page 306*).

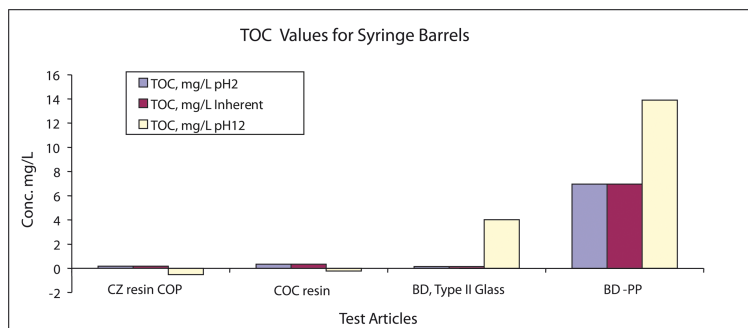


**Figure 12.3** Comparison of total organic carbon as an extractable from syringe barrels. *Source:* Reproduced from Ref. 6 (see page 307).

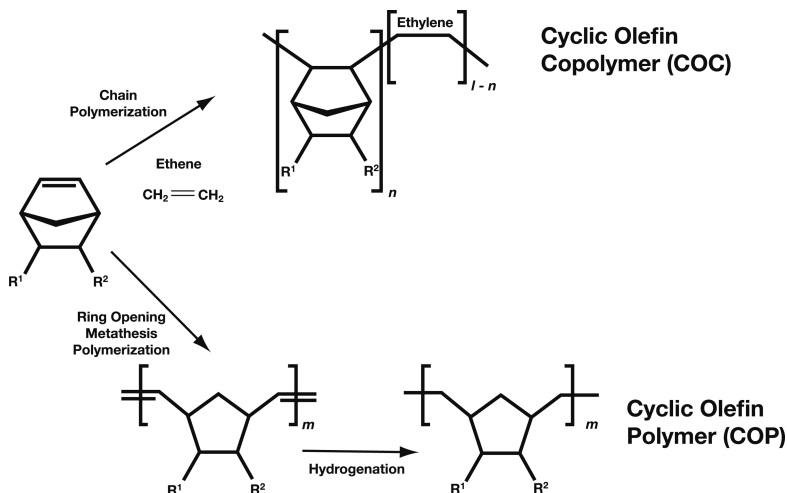


**Figure 2** Process of polymerization in the development of cyclic olefin polymers/cyclic olefin copolymers. Source: Reproduced from Ref. 2.

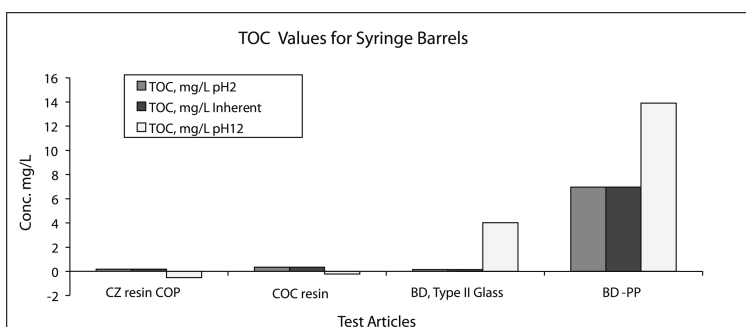


**Figure 3** (See color insert) Comparison of total organic carbon as an extractable from syringe barrels. Source: Reproduced from Ref. 6.

the resultant manufactured components, as well as the parenteral products that are delivered to the end user. The polymers have good melt flow properties that readily lend themselves to plastics processing, for example, molding and thermal forming. The polymers exhibit a high impact and break resistance, and they form an excellent moisture barrier (2–5). Additionally, they possess good chemical resistance to acids, bases and alcohols. These polymers are sterilizable by autoclave, ethylene oxide and radiation sterilization processes. As with most plastics in comparison with glass, the number of potential compounds that may be an extractable or leachable is higher for plastic than for glass because the number of components in the formulation is higher. These compounds are organic, whereas glass potential extractables are inorganic. Plastic vendors can provide a list of potential extractables developed with suitable extracting solutions. A decision may then be made on which potential extractables should be studied as leachables during stability testing. Preliminary studies have shown that, when compared with other materials that are used for parenteral applications, COP and COC exhibit very low extractables (Fig. 3). When studied for total organic carbon (TOC) extracted from syringe barrels at various pH levels, the

**Table 1** Features of Cyclic Olefins for Parenteral Drug Delivery

| Key benefits                                               | Drawbacks                                                                              |
|------------------------------------------------------------|----------------------------------------------------------------------------------------|
| Glass-like transparency                                    | Gas and moisture barrier properties are less than glass but better than other plastics |
| Sterilizable (via autoclave, radiation and ethylene oxide) | Sensitivity to scratches                                                               |
| High break resistance                                      | Short-term discoloration due to radiation                                              |
| Excellent moisture barrier                                 |                                                                                        |
| Biocompatible (inert, low binding, and ion extractables)   |                                                                                        |
| Design flexibility and excellent dimensional tolerances    |                                                                                        |
| Good chemical resistance                                   |                                                                                        |

data shows very low extractable for COP (CZ) and COC compared with PP and glass (6,7). On the basis of this data and other information available, COP and COC are considered to be ideal plastic packaging containers for SVP. There are some drawbacks, however. Understanding these drawbacks will be important in the selection of cyclic olefins as a packaging system (Table 1). These plastic containers cannot match the barrier properties of glass to oxygen and moisture ingress, although they are much superior to other plastics, including PP, polystyrene and polycarbonate (PC). For oxygen-sensitive compounds, this may be a concern. Suitable secondary packaging can prevent moisture loss or oxidation, with the addition of a moisture absorbent or oxygen scavenger material.

*High-density polyethylene (HDPE):* The polymer is based on a simple repeating carbon/hydrogen molecule that branches out during polymerization to form a polymer with a high degree of regularity. This regularity creates the formation of crystal lattice structures. Polyethylene (PE) is recognized as having a high degree of crystallinity. During polymerization, the amount of branching that occurs during the process will determine the overall density and crystallinity of the resulting PE. As a result of their relatively high degree of crystallinity as compared with lower-density PEs, HDPEs have greater tensile strength and stiffness and have a higher melting point than the low-density polyethylene (LDPE) resins. Another important property is excellent chemical resistance, a characteristic of all polyethylene grades. HDPE is typically used for low-to-medium barrier medications, such as bottles, closures and in some cases, secondary packaging of parenterals and blister packs for solid dosage forms. The material is characterized by strong impact resistance, chemical resistance, drug compatibility for oral dosage forms and temperature tolerance. Both HDPE and LDPE are used to form containers by blow-fill-seal technology, primarily for ophthalmic and nasal/respiratory drugs, but also have been used for both SVP and LVP products.

*Polypropylene (PP):* PP is the leading plastic employed in containers, disposable syringes, PFS and closures. PP is a linear, high crystalline polymer, made of carbon and hydrogen in a very orderly fashion. The regularity of its structure imparts the high degree of crystallinity found in most commercially available PP. Within the crystal array, the methyl groups impart stiffness to the polymer, making it different from its close relative, polyethylene. PP exhibits a high tensile strength, which is the ability to withstand forces tending to pull apart or distort the material, and is more rigid than HDPE. High tensile strength, in conjunction with a high melting point of 165°C, is particularly important for packaging drugs. Consequently, the material has the ability to withstand higher temperatures of autoclave sterilization for a limited number of cycles. PP is also resistant to chemical attack from organic solvents and strong acids and bases at room temperature. Because of the level of crystallinity present, it is not possible to achieve the optical clarity found with cyclic olefins: the crystal lattice sites tend to refract light, which imparts haze. The resin generates significant demand for the manufacture of blow molded bottles, pouches, laminates and plastic containers. Because of its improved moisture resistance and effective chemical resistance, PP is

typically used in disposable containers or delivery systems. It may have poor impact resistance at lower temperatures and increased extractables, and its translucency limits its role in the storage of parenteral drug and biological products for long duration.

*Polyethylene terephthalate (PET):* PET is a high-quality thermoplastic polyester that offers good barrier protection, chemical resistance and processing properties. It is typically used in packaging drugs that may require barrier protection as in blister packs and blow molded containers. It is cost competitive with HDPE and PVC and is used in development of bottles and blister sheeting. PET is polyester that is a condensed polymer prepared from ethylene glycol (EG) and either terephthalic acid (TPA) or the dimethyl ester of terephthalic acid (DMT). The EG monomer is prepared using ethane as feedstock and the TPA is manufactured using paraxylene as feedstock. TPA can then be purified by reaction with methanol to form the DMT. PET can exist in an amorphous state, an oriented and partially crystalline state and a highly crystalline state. Because of its low glass transition temperature, PET cannot tolerate autoclave sterilization. The material does hold up well to gamma radiation, making it the preferred method for sterilization. Ethylene oxide sterilization is also acceptable with PET resins. PET film may potentially be used as a coextruded layer of LVP bags (replacing use of PVC resins).

*Polycarbonate (PC):* PC is known for its mechanical properties and higher clarity with poor barrier properties. PC-based polymers are aliphatic molecules and are synthesized in various forms. These aliphatic PCs become extremely soft in the 40°C to 60°C temperature range. Bisphenol A PC is extremely stable and virtually nondegradable under physiological conditions. PC can be processed readily, possesses high mechanical strength and is very shatter resistant. PCs are used extensively as bottles and containers for parenteral applications. PC resin contains repeating aromatic rings in its main chain structure. The material is a polyester of carbonic acid and is generally produced using an interfacial reaction between dihydric or polyhydric phenols and a suitable carbonate precursor such as dichlorocarbonate. Currently most PCs are produced with a reaction between bisphenol A and carbonyl chloride in an interfacial process. Other polyhydric phenols are sometimes used to form copolymers for special end uses. The material is well suited for the injection molding process. PC shows excellent creep resistance over a broad temperature range, enabling its use in applications previously open only to thermoset materials. There are, however, some areas where PC resins are inferior. PC materials have limited chemical and scratch resistance and a very high water transmission rate when compared with other plastics. The resin also has a tendency to yellow with light exposure and with exposure to radiation sterilization.

*Polyvinyl chloride (PVC):* Less popular in parenteral packaging, PVC is prepared by polymerizing a gas, vinyl chloride or monochloroethylene, in the presence of organic peroxides or inorganic persulfates as initiators. The length of the molecular chain and the structure of the side chains are altered by the temperature, pressure and the nature of the initiator. PVC's growth in pharmaceutical packaging is much slower compared with its peers because of environmental concerns. This includes the formation of dioxin when PVC is incinerated. Additionally, di(2-ethylhexyl) phthalate (DEHP) plasticizers are used in the production of many PVC materials. These types of phthalates, which are known to leach out of PVC containers, may have potential health risks. Growth has slowed in this area, which probably reflects preferences for better performing and safer plastics.

*Multilayer plastics:* Plastic bags commonly used for LVP generally consist of between three and five layers of plastic film consisting of two or more different resins. Similarly, plastic film used for blister packaging of tablets is also multilayered. The purpose is to produce a plastic film that combines the best properties of each film including good clarity, excellent flexibility and durability, which also is a strong barrier to water vapor transmission.

*Plastics fabrication:* There are many processes used to convert plastic resins from pellets into desired shapes or configurations. This is a brief description of the plastic molding

processes. All plastic processes are similar in the use of three basic elements to convert the resin from a pellet to its processed shape.

1. *Heat*: excites the molecular structure to allow free movement of molecules
2. *Pressure*: forms the free-flowing polymer into a desired shape
3. *Time*: allows the transfer of heat into the plastic followed by time for removal of heat (cooling)

*Extrusion of plastics*: The process of extrusion involves melting a plastic and forcing it through a die under pressure to form a desired shape. There are several types of extrusion, depending on the die arrangement used to form the plastic. The three most widely used for parenteral packaging are flat-sheet extrusion, profile-tubing and blown-film extrusion. Flat-sheet extrusion is a versatile process, with the capability to produce sheet stock over a wide range of thicknesses from a wide range of resins. The process may also be used to produce coextruded sheeting where two or more different resins are brought together in the die manifold from two or more extruders. Flat-sheet extrusions can be used for blister packaging and form, fill and seal packaging. Clear grades of plastic that have a high degree of stiffness are generally preferred for extrusion processing. Another application for this process is the production of LVP containers.

*Injection molding*: Injection molding is a process used to convert resin from a melt into a molded shape using a mold pattern to form the part. Injection-molded products are replacing materials such as glass, metals and paper in many areas of parenteral drug packaging. The development of newer plastic resins, combined with improvements in the injection molding process, is setting the stage for these changes. For example, materials such as CZ resin have been used to develop larger containers such as the 1-L bottle by injection molding. Many of these newer resins are used for drug delivery systems that are replacing products traditionally made from glass. In this process, plastic resin is melted using the extrusion process and is injected into a mold where the resin is cooled enough to be removed in a solid state. Like the other plastic processes, heat, pressure and time are used in each of the steps to produce a molded product. Injection-molded items are finding many uses in parenteral drug packaging. The injection molding process is also used to produce components such as IV spikes and IV administration sets.

*Blow molding*: The blow molding process has grown rapidly over the past three decades. The two types of blow molding in use are extrusion blow molding and injection blow molding. A uniform tube of heated resin with one end closed is formed during the extrusion blow molding process and is moved into a mold where the two ends are pinched off, and the material is blown outward into the shape of the mold. The injection blow molding process is similar in concept except that is a two-step process. A preform is molded using a first-stage mold and the principles of injection molding. The form is then transferred into a second mold, and blown outward using pressurized air to form the container. Containers produced for health care applications, such as tablet bottles, are made primarily using the injection blow mold process. With small containers, this process is more cost effective than extrusion blow molding because it is capable of handling a large row of preforms at one time. Extrusion blow molding lends itself to larger containers where it becomes more economical and practical to eliminate the preform step. The blow molding process enhances the physical, chemical and barrier properties of certain materials, for example, PET, because it creates a high level of bi-axial orientation of the polymer. CZ, Zeonex and Topas resins also use the blow molding process to manufacture vials.

## VIAL SYSTEMS

*Market considerations*: A vial is a SVP container with a stopper and a seal, intended to package liquid or a dry powder formulation for either single or multiple doses. Glass vials, typically made of type I glass, are most commonly used as vials for parenteral

applications. Recently there is increased interest in the use of newer plastics, particularly the cyclic olefins, as parenteral vials as they provide clarity and inert surfaces for biopharmaceutical and biological applications. When combined with plastic's inherent break-resistant attribute and the need for biologics to be stored and transported at lower temperatures, the future of cyclic olefin based plastics appears bright. Cyclic olefin polymers (COP) and copolymers (COC) are considered to be an ideal plastic for vial systems because they have glass-like clarity and suitable physicochemical properties and the ability to be sterilized.

The vendors in this area may be divided into those that manufacture the COP and COC resins such as the Zeon Corporation and Topas Advanced Polymers and companies that convert the resin into parenteral containers such as Schott Forma Vitrum that offers a range of sizes of both syringes and vials made out of COC under the brand name Schott TopPac<sup>®</sup>. Daikyo Seiko, Ltd. of Japan has used a proprietary COP resin to produce a range of sizes of conical, flat-bottom vials and larger screw-top containers, under the brand name of Crystal Zenith. West Pharmaceutical Services, Inc. (West) partners with Daikyo to codevelop, market and sell sterile and nonsterile CZ vials. As a result of the anticipated growth, the suppliers of resins and products have made significant investments to their supply chain to maintain continuity of supply. Rexam offers a new generation of multilayered plastic vials called MLx that are being used as a container with improved barrier properties. The COC vials produced by Aseptic Technologies represent a newer approach to vial handling and filling called the Crystal<sup>®</sup> technology, licensed from Medical Instill Technologies (Table 2). The vials and stoppers are molded and assembled immediately under clean conditions and gamma sterilized. Filling is achieved by piercing the thermoplastic closure and then immediately resealing the puncture with a laser. COP and COC vials have been tested and used to replace glass in various pharmaceutical parenteral applications. This is because glass contains free alkali oxides and traces of metals and, at higher pH conditions, can undergo delamination, thus affecting the stability of the drug product (8,9). Proteins and peptides can be adsorbed on a glass surface and can either be denatured or become unavailable for treatment (10,11). Glass particles can promote protein particulate formation, and glass is also more likely to break under processing, storage or transportation of biopharmaceutical products, especially at lower temperatures. In these areas and more, plastic vials have made clear in-roads in the pharmaceutical drug delivery market.

*Protein and peptide adsorption:* Numerous studies have addressed the adsorption of proteins to packaging containers. This interaction of proteins and peptides with the surfaces of storage containers can result in their loss and destabilization (12–14). Although the amount bound is typically low, this problem can be acute at low protein concentration where a substantial portion of what is usually assumed to be solution-state protein may actually be adsorbed to the container walls. Although protein

**Table 2** COP/COC Packaging Systems for Parenteral Delivery

| Company                    | Trade-name/type of cyclic olefin              | Delivery system/sizes             |
|----------------------------|-----------------------------------------------|-----------------------------------|
| Amcor/Alcan Packaging      | COC                                           | Vials 2 mL and 5 mL               |
| Aseptic Technologies/Rexam | Crystal <sup>®</sup> /COC                     | Closed vials <sup>a</sup> 1–50 mL |
| Becton Dickinson           | Sterifill <sup>®</sup> /Crystal Clear Polymer | PFS <sup>b</sup> 5–50 mL          |
| Daikyo/West                | Daikyo Crystal Zenith <sup>®</sup> /COP       | PFS <sup>b</sup> 0.5–100 mL       |
| Gerresheimer/Taisei Kako   | Clearject <sup>®</sup> /COP                   | Vials <sup>a</sup> 0.5–1000 mL    |
| Rexam                      | MLx/COC, COP                                  | PFS <sup>b</sup> 1–20 mL          |
| Schott                     | Schott TopPac <sup>®</sup> /COC               | Multilayer vials & bottles        |
|                            |                                               | PFS <sup>b</sup> 0.5–50 mL        |
|                            |                                               | Vials 2–100 mL                    |

<sup>a</sup>Presterilized vials and containers available

<sup>b</sup>Presterilized formats available

*Abbreviations:* COP, cyclic olefin polymer; COC, cyclic olefin copolymer; PFS, prefillable syringe.

binding is protein and formulation dependent, studies have shown a trend toward less protein adsorption to cyclic olefin containers. Burke et al. (15) compared glass vials with plastic vials made of polyester, PP and nylon for protein binding. Although no clear conclusion could be drawn on the binding characteristics of these primary packaging materials, it was observed that the degree of binding was highly protein-dependent. Qadry et al. (11) showed less protein binding to plastic CZ vials compared with type I glass, suggesting that the CZ vial is a potential candidate for an alternative material to the glass vial because of low affinity of proteins to bind to its surface. Eu et al. (16) compared the level of adsorption between glass and CZ vials and showed that a model protein preferentially adsorbed to glass vials compared with CZ vials. The authors used gold nano-particle staining techniques for a visual comparison of protein adsorbed to vial surfaces, but this technique does not permit quantitation of the amount of protein adsorbed to the surface. Waxman et al. (17) developed methods to quantitate protein adsorption on vial surfaces. One method uses the protein stain colloidal coomassie, which binds to protein adsorbed to vial surfaces and can be eluted and quantitated spectrophotometrically; the other method involves hydrolyzing the protein adsorbed *in situ* and quantitating the peptides released fluorometrically after reaction with fluorescamine. These approaches allow testing over a much broader range of protein concentrations without the use of radiolabeling. Using these methods, the authors confirmed that binding occurs rapidly and the amount of protein adsorbed per SVP vial is typically in microgram quantities. Protein adsorption to CZ vials was found to be independent of ionic strength, likely because of its hydrophobicity; in contrast adsorption to glass vials was inhibited with increasing ionic strength, indicating the effect of electrostatic interaction with glass containers. In our opinion, protein adsorption is clearly protein dependent, and testing needs to include glass and plastic containers with elastomer influence, before optimizing the drug formulation and container closure system.

*Storage and transport at low temperatures:* In the area of cell therapy, stem cell research holds significant promise for development of innovative therapies for many unmet or partially met disease treatments. As products enter clinical development stages, there is need for clean, clear, biocompatible, low extractables containers. The ideal vial-based system should be a suitable package to store and transport cell therapy products at lower temperatures; it should be suitable for commercial filling and meet pharmaceutical quality requirements. PP is a plastic resin that has been used for decades for various packaging applications including bottles, pouches, prefilled syringes, tubes and containers. Plastic resins have made minimal headway in the area of parenteral vials because of various quality attributes. A study investigated the use of CZ plastic vials for storing and shipping cell therapy products at low temperature ( $-85^{\circ}\text{C}$ ) or cryopreserved ( $-196^{\circ}\text{C}$ ) for six months using 0.5, 5.0 and 30 mL volume vials (18). Vials were tested for durability and integrity of a filled vial using a 1-m drop test, and for the ability to maintain viability and functionality of stem cells over the time of storage. No evidence of external damage was found on vial surfaces in the 1-m drop test. Post-thaw viability using dye exclusion assay was  $>95\%$  and stored cells exhibited rapid recovery two hours post-thaw. Cultures were  $\sim 70\%$  confluent within five to seven days, consistent with nonfrozen controls and indicative of functional recovery. CZ vials were durable and allowed for preservation and maintenance of cell viability and functionality, showing that these vials offer significant benefits to storing and transporting biological and biopharmaceutical products for storage, clinical and commercial applications.

*Lyophilization and reconstitution:* Cyclic olefin based plastics COC and CZ vials have been extensively studied for packaging lyophilized products. Freeze-drying in a plastic vial brings added advantages, especially when cytotoxic and biohazard products need to be packaged. Crystal technology, developed by Aseptic Technologies, applies the closed-vial technology for lyophilization (19) and for liquid fills. After filling closed vials using a piercing needle, a small disposable device called the penetrator reopens the orifice and, when the lyophilization chamber shelves move, the penetrator is

pushed down, releasing the water vapor. Lyophilization of mannitol and arginine was studied in Daikyo's CZ vials and compared with molded glass and tubing glass vials. The crystallinity of mannitol in CZ vials was either greater or comparable to glass vials. There was thermal homogeneity within the CZ vial during the lyophilization cycle, providing more uniformity within the cake (20). Despite the fact that COC and CZ plastics provide a high moisture vapor barrier, it is always recommended that a secondary packaging barrier such as an aluminum pouch or a blister pouch with aluminum lidding and very low water vapor thermoformable film be used to assure adequate shelf-life protection for lyophilized products. For liquid fills in COC or COP, additional barriers are not necessary because of the low moisture vapor transmission rate of cyclic olefins.

Many drug candidates are marketed in lyophilized form to maintain shelf-life stability and require reconstitution prior to administration. Some of these products, including treatments for hemophilia, multiple sclerosis and autoimmune diseases, may be administered in a home environment. Traditional reconstitution requires the use of multiple vials and needles, which can prove to be complicated for patients or untrained personnel, and may increase chances for needle stick injuries. In recent years, there has been an increasing use of safer and more convenient reconstitution devices made out of plastics. These provide simple methods to reconstitute products without the use of needles and may also improve the effectiveness of the reconstitution process and compliance with the dosing regimen. There are several types of reconstitution systems designed to connect the drug container (typically a vial) to a diluent container (either a vial or a prefilled syringe). Plastic reconstitution devices are sterile, nonpyrogenic, biocompatible and fully supported by appropriate regulatory filings (21). They are designed for short-term contact with the drug product, and can be manufactured from a variety of medical grade plastic materials, such as PC and polyolefins, with the precise material selected on the basis of functional requirements. An example of a plastic reconstitution device, a vial adapter, is shown in Figure 4. For most vial adapters, and other components where a plastic spike is required, PC is used as it provides the appropriate balance of rigidity and sharpness to optimize spiking performance and attachment to the vial. Other materials, such as HDPE, can be used for components within the system where a stopcock system is required. These component devices are packaged in a rigid blister, often made from PET, to maintain sterility and to enable ease of handling and protection of the device during use. Plastic vial adapters can provide safe, easy to use and cost-effective diluent transfer to a lyophilized drug vial. The adapter snaps to the neck of the standard vial after the plastic button has been removed. A plastic spike pierces the stopper; needles are not



**Figure 4** Vial adapter. Source: From Medimop Medical Projects Ltd.

used. Plastic vial-to-vial transfer systems also offer a similar level of simplicity and cost-effectiveness through a double-spike adapter that connects to the top of each vial (lyophilized drug and diluent). This is an ideal solution for connecting vials of different sizes. These advanced plastic reconstitution systems offer several benefits, including ease of use by patients and caregivers; protection against drug spray-back and accidental needle stick injuries; needleless reconstitution and transfer. They may also help drug manufacturers reduce the amount of overfill in the drug vial (22).

*Process considerations:* Glass vials are washed, depyrogenated and sterilized by heat before they are filled. Plastic containers cannot be heated to high temperatures for depyrogenation, therefore alternative methods are used. Plastic molding and packaging in environmentally controlled clean rooms usually produce products that have very low bioburden and low particulate level. Nonsterilized vials undergo water-for-injection rinses for depyrogenation, followed by sterilization using autoclave, radiation (gamma or e-beam) or ethylene oxide. All handling operations are designed to avoid scratching the vials' outer surfaces, as plastics have a tendency to scratch. To minimize scratching, care is usually taken not to stack vials too tightly in processing. During autoclave sterilization processing, hazing of the plastic walls is known to occur. This is where moisture gets trapped during processing and may take a few days to diffuse out, but the clarity and integrity of the vial is not compromised. Vial spacing during the autoclave sterilization process may help mitigate this effect. For vials in a ready-to-use format, vendors offer sterile vials and containers. Sterile vials or containers are nonpyrogenic and have a very low particulate level, and could be used to store and transport drug products as early as first-in-human studies. Most commercial filling companies can accommodate filling of COP and COC plastic vials if care is taken to accommodate the characteristics of plastic vials. During filling of plastic vials, guide rails and vial handling change parts should be covered with a material that will limit scratching of the vials. The speed of the filling line may also need to be adjusted to accommodate filling of the lighter plastic vials.

**PREFILLABLE SYRINGE SYSTEMS**

*Market considerations:* In the current global market, PFS comprise more than 2.0 billion syringes per year in development and use. The origin of the prefilled syringes' rise as the preferred container was an extremely successful market introduction of syringes for heparins by Sanofi and Rhone Poulenc-Rorer (Sanofi-Aventis) in Europe in the early 1980s. The PFS market has now exploded because of several factors: the growth of biopharmaceuticals; the need to eliminate overfills; precision of delivery volume; convenience of delivery, cost-effectiveness; elimination of dosage errors or a combination of these factors (23–26). Glass continues to dominate the PFS markets with a significant market share; however, plastic PFS are beginning to make advances, especially where glass has been unsuitable as a delivery system. PFS have been in use as larger volume containers for x-ray contrast media or medical devices such as hyaluronic acid derivatives (23). In the last decade, however, pharmaceutical drug products have been approved for use with prefillable plastic syringes, including a new chemical entity for oncology and a peptide drug product for the treatment of osteoporosis (Table 3).

| Table 3 Global Regulatory Approvals of Drug Products in Cyclic Olefin Polymers/Cyclic Olefin Copolymers |                              |                              |
|---------------------------------------------------------------------------------------------------------|------------------------------|------------------------------|
| Therapeutic area                                                                                        | Plastic packaging            | Approvals                    |
| Anemia                                                                                                  | Cyclic Olefin                | Japan                        |
| Osteoporosis/Oncology                                                                                   | CZ vials                     | United States, Europe, Japan |
| Antifungal                                                                                              | CZ vial                      | Japan                        |
| Osteoporosis                                                                                            | CZ syringe                   | Japan                        |
| Radiology                                                                                               | CZ syringe                   | Japan                        |
| WFI product (for thrombolytic drug)                                                                     | TopPac <sup>®</sup> syringes | Europe                       |

*Abbreviation:* CZ, Daikyo Crystal Zenith<sup>®</sup>.

Although not reaching the adoption level of glass syringes, plastics syringe systems continue to gain strong acceptance from pharmaceutical manufacturers because of recent improvements in design, composition and manufacture. Plastic syringes were historically made out of PP, however, recent developments in the area of thermo-elastic polymers, such as cyclic olefins, have made substantial headway in the use of plastics as a PFS system. COP is as clear as glass, has low extractables, is less reactive and has better barrier properties compared with PP. Multiple vendors offer different sizes of syringes in sterile nested configuration or as nonsterile bulk syringes. Cyclic olefin plastic barrels are formed by injection molding under clean conditions and assembled in similar conditions, primarily to maintain a high level of cleanliness. Plastic syringes are sterilized either by autoclave, radiation (gamma or electron beam) or by ethylene oxide, but not by dry heat, and are offered as assembled sterile syringes that are ready for filling. The molding process also provides a greater degree of flexibility to include design features such as a plastic finger grip that can be combined with a back stop to prevent the piston being pulled out of the barrel.

To meet the need for lubricity and sealability, syringe manufacturers use silicone to coat the glass barrels and elastomer components. Silicone facilitates ease of movement of pistons in filling and stoppering equipment, and allows pistons to glide smoothly on activation of syringes. Silicone, however, can interact with drug formulation components (27,28). Recent developments to minimize free silicone include baking silicone at high heat onto the glass barrels, thereby minimizing the amount of free silicone that can interact with drug product. Advances in elastomer closure technologies have produced closures that do not require siliconization because of a special polymer lamination applied to the outer surface of the piston, thereby offering a silicone oil-free PFS system such as the Daikyo CZ syringe system. The syringe system includes a plastic COP barrel, nozzle cap and piston laminated with a fluoro-polymer lamination, Flurotec<sup>®</sup>, and requires no silicone for consistent functionality. Flurotec is a lamination technology using copolymer film of polyethylene tetrafluoroethylene (PTFE) or ethylene tetrafluoroethylene (ETFE). Helvoet (Omniflex<sup>®</sup> 3G) pistons also have a fluoro-polymer coating, however, these typically are coated with a sprayed-on polyvinylidene fluoride (PVDF) and will need siliconization for use with glass or plastic barrels. Use of these coated stoppers provides lubricity for machinability and reduces piston clumping in feeder bowls. Additional benefits, depending on the coating used, include a decrease in particle generation and a reduction of extractables from the elastomer (27,29).

*Improving protein stability:* Growth in the pharmaceutical industry is expected to be driven by biotechnology products and vaccines. This will be associated with significant challenges in the formulation development of proteins such as monoclonal antibodies, as they are typically administered in high doses. High-concentration proteins have a propensity to interact with each other and with the packaging components and cause protein instability, especially when the volume of delivery is approximately 1 mL. Challenges with glass PFS typically encompass breakage, presence of particulates, glass reactivity to the drug product and potential leachables including silicone, tungsten and adhesive. A plastic PFS offers options to solve such challenges. A plastic PFS can eliminate silicone, tungsten and adhesive, depending on the quality attributes of the entire prefillable system. For instance, the CZ insert needle system uses no silicone for syringe functionality, no tungsten (commonly used during the glass syringe forming process) and no adhesive (commonly used to hold the staked needle in place).

There are reports that the detachment of silicone oil in water-filled syringes is possible (30) and can result in particulate matter and clouding phenomenon. Silicone oil interaction has been suspected as being responsible for aggregation in protein pharmaceuticals. Several publications in the 1980s have discussed this issue, especially with regard to the aggregation of insulin in disposable siliconized plastic syringes (31–33). Surfactants such as polysorbates have been used extensively to prevent/inhibit protein surface adsorption and aggregation under various processing conditions (34,35). One consequence with using polysorbates in protein preparations

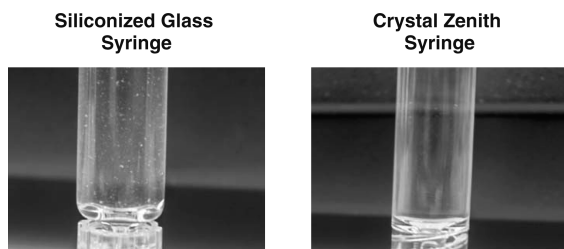


**Figure 5** Aggregates in siliconized syringes and silicone-free syringes.

is their potentially adverse effect on protein stability, including the oxidative damage of the residual peroxides in Tweens, which are generated during processing or storage (36). This can pose a serious problem affecting the shelf-life of products. Polysorbates and their concentration should be selected carefully. In addition, the choice of a suitable container will help mitigate significant risks of protein aggregation caused by silicone oil. The propensity of proteins to aggregate when silicone oil is present in formulation was further investigated by Esfandairy et al. (37). Silicone oil-induced aggregation of proteins was studied on silicone oil-free plastic syringe systems and siliconized glass PFS systems. The study included model proteins at low concentrations of 0.35 mg/mL to as high as 25 mg/mL. Although no unambiguous generalization was drawn at lower concentration, there was a clear effect at protein concentrations as high as 25 mg/mL. Effects on protein aggregation with silicone oil were observed during air shipment of samples, caused by effects of agitation and vibration. The study showed that the extent of aggregation in silicone oil-free CZ syringes was less compared with siliconized glass syringes under the conditions examined (Fig. 5). The study recommended that the susceptibility of therapeutic proteins to silicone oil-induced aggregation be investigated on a suitable container closure system before finalizing stabilized formulations and container selection.

Various methods are used to siliconeize syringes, including stationary nozzles and diving nozzles. Recent studies have shown that (16) silicone oil distribution is often nonuniform, leaving certain areas of the syringe surface without any silicone oil. The low or inconsistent silicone oil coating can have a significant impact on the piston travel/glide forces, especially in the use of autoinjectors. In 2006, lots of Neulasta<sup>®</sup> delivered by an autoinjector containing a glass PFS were recalled in a number of European countries because of problems with slow or incomplete delivery of the drug (38). Areas of nonuniformity cause travel forces to increase, causing failure or incomplete injection. In addition, there has been significant attention to tungsten as a leachable present in glass PFS. These reports discuss tungsten-based particulate matter leaching and interacting with the protein drug product (39). Tungsten pins are typically used to keep the fluid path open at the nozzle end of the syringe at around 1200°C during the glass syringe forming process. Upon cooling, a needle is staked-in with adhesive, to make a glass PFS with a staked needle. The residual tungsten had migrated into the drug product and caused the protein to form protein-tungsten aggregates. Although this appears to be protein specific, it is important to test for protein-tungsten interaction at an early stage of drug development. In another case, a residue was observed in a PFS during the manufacturer's inspection. Upon investigation, the material was identified as poly (metaxylylene adipamide), a component of the glass fiber pin use by the syringe developer during the needle assembly and curing process (40). Such concerns may be mitigated with the use of COP/COC syringes. Silicone oil-free CZ syringes have been shown to have consistent travel forces over time and temperature. The dimensional tolerance of plastic syringes and consistency of syringe functionality will provide a predictable operation of a drug product-filled autoinjector. CZ syringe systems have no tungsten as a leachable because the needle is insert-molded, avoiding the need for tungsten pins and adhesive, which

are typically used with glass staked-needle syringes. The manufacturer has developed a PFS system intended for biopharmaceutical drug delivery that is free of silicone oil, tungsten and adhesive (41).

*Process considerations:* In the current market environment, presterilized, ready-to-fill syringes are increasingly more prevalent. PFS are now available in sterile and ready-to-used formats. As glass PFS are already being filled using tubs, a switch to PFS in a similar tub and nest configuration has been achieved using the same filling machines, with minor modification and change parts to accommodate plastics. Most commercial filling companies can accommodate plastic syringes. The control of dimensional tolerances of plastic syringes far exceeds that of glass syringes and, because they are less prone to breakage and shattering, plastic prefilled syringes are generally easy substitutions for glass PFS on modern filling/processing equipment. There are, however, some physical differences between glass and plastic that should be considered before running plastic PFS on a filling/processing line designed for glass PFS. Plastic syringes are prone to scratches and cosmetic defects from contact with metal surfaces in processing equipment and the weight of plastic PFS is less than their glass equivalents. Scratching may create an unacceptable level of cosmetic defects. Lighter weight syringes can cause problems when gravity is responsible for syringes settling into place in processing equipment. The issues of weight and scratching often manifest themselves when metal centering devices are used to hold and center PFS during filling and stoppering processes. These problems can be overcome by reengineering some parts of filling and processing equipment or by running equipment at slower speeds. It is expected that, as the use of plastic PFS becomes more prevalent, manufacturers of filling/processing equipment will design equipment that performs equally well with both glass and plastic PFS.

There are various processes for filling and stoppering PFS. These include filling and stoppering using vent-tube, or vacuum fill or/and stopper placement. Vent-tube is more commonly used for uncoated or partially coated pistons intended for glass and plastic PFS. For coated pistons, vacuum placement works well as the procedure uses differential pressure rather than force to eliminate wrinkling of the lamination. Vacuum placement is particularly important for laminated pistons, especially in CZ syringe systems, which use a piston that is coated on the drug product contact and syringe barrel contact surfaces. The piston provides lubricity for efficient piston release and consistency of travel forces for a silicone oil-free system. An option offered at Hyaluron Contract Manufacturing, Burlington, Massachusetts, for filling PFS, BUBBLE-FREE FILLING<sup>®</sup>, uses online vacuum filling and online vacuum stoppering (42). The primary advantage is the reduction of the air bubbles that exist between the product and the stopper in traditionally filled syringes. This may help mitigate concerns regarding oxidation of the product.

## **LARGE-VOLUME PARENTERALS**

LVP refer to sterile diluents, electrolytes, irrigating fluids, blood derivatives, nutritional preparations and premixed injectable drugs administered in quantities of over 100 mL. LVP are packaged in semi-rigid plastic containers, flexible minibags and, to a lesser extent, glass containers. Three major global manufacturers of LVP include Baxter, B. Braun and Hospira. The sterile formulation of LVP necessitates the use of containers with good barrier properties and sizes of semi-rigid plastic IV containers range from 250 mL for biologicals and nutritional up to 4 L for standard diluents (such as sodium chloride and dextrose).

Minibags are used for administering lower-volume parenteral admixtures, and most premixed IV solutions are packaged in specially designed minibags. IV minibags usually contain 50- or 100-mL volumes of solution and are made of PETG, PP and various polyethylene-based coextrusion. These containers provide a sterile format consisting of a drug mixed with an appropriate diluent solution. Premixed minibags eliminate the need for independent admixture preparation and provide significant time, labor saving and waste

reduction advantages. Most major parenteral drugs are now available in this format, including drugs for antibiotic, analgesic, anticonvulsant, cardiovascular, psychotherapeutic and respiratory preparations. Some solutions packaged in the container must be stored frozen and thawed no more than 24 hours prior to use.

Historically, PVC was the leading material employed in the production of LVP configurations. However, this trend has changed because of potentially adverse patient reactions to a plasticizer used to stabilize the resin. Known as DEHP, the plasticizer has been linked to infertility and hormonal imbalances in laboratory animals. Regulatory authorities have recommended that all medical products based on PVC and DEHP be either adapted to alternative materials or include a label warning about the plasticizer. In response, the producers of IV solutions have adopted newer plastics for their containers. B. Braun Medical eliminated the use of PVC in IV packaging. The company's Excel<sup>®</sup> and PAB<sup>®</sup> IV containers now include specialized PP materials. Newer, higher-grade plastics, such as PETG copolyester, are being used for minibag applications to keep solutions stable, including Baxter's and Hospira's products. Baxter International recently introduced Buminate<sup>®</sup> human albumin solution in a Galaxy<sup>®</sup> minibag that is composed of proprietary, high-barrier plastic film. The new Galaxy package can provide a shelf-life of two years and eliminates the need for preparing admixtures in hospital pharmacies. Hospira's ADD-Vantage<sup>®</sup> system is a specially designed diluent container that connects to a vial. Once the vial is affixed to the container, the active drug blends with the diluent and creates the finished IV solution. The ADD-Vantage system allows the IV solution to be mixed directly at the site of administration. Another innovative IV minibag system is the Duplex<sup>®</sup> Drug Delivery System developed by B. Braun. Duplex is a dual-compartment flexible plastic IV bag that stores unit dosages of drug powder and diluent separately in the same container. The health care professional squeezes the bag to break the quick-release seal, mixing the drug and diluent just prior to administration. Designed to simplify the intravenous delivery of antibiotics, the Duplex container reduces product waste, eliminates the use of vials from the preparatory process, and is equipped with a standard linear bar code to reduce dosage errors and track inventory.

X-ray contrast media is also packaged in a range of volumes from 50 to 500 mL in both plastic and glass containers, with the 500 mL containers labeled as pharmacy bulk packages. PP prefilled syringes and prefilled PP cartridges designed to fit a specific range of power injectors for computed tomography are available (43). Another design of a prefilled cartridge called REDIFLOW<sup>™</sup> is available in a clear plastic to fit a second range of power injectors for computed tomography as well as PP bottles (44).

## PLASTICS AS DISPOSABLE SYSTEMS FOR BIOPROCESSING

*Market considerations:* Plastic packaging systems for LVP drugs are facing increasing scrutiny. All packaging systems, stainless steel or plastic, need to provide and meet the same requirement for protection, compatibility and safety as those used for SVP (45). This section addresses the use of plastics as disposable bags in packaging large-volume drug substances or drug products in bioprocess development and fill/finish operations (46,47).

According to the report released by the Tufts Center for the Study of Drug Development, Outlook 2009 (48), there are more than 200 new monoclonal antibodies in development worldwide, and the FDA has approved 22 monoclonal antibodies. To support development of these biologics, the biopharmaceutical manufacturing industry is rapidly adapting to disposable systems. Single-use bioprocess systems referred to as disposables have become common in the industry. Disposable systems have gained increased acceptance for manufacturing-scale storage and processing of recombinant proteins and monoclonal antibodies in liquid and frozen forms (49,50). This is driven primarily by the key benefits plastic disposable containers offer over stainless steel containers. These include reduced capital expenses (stainless steel vessels, cleaning and sterilization validations), minimizing cross contamination, flexibility in manufacturing and easier scale up (51,52).

Disposable technology employs a multitude of plastics to customize processing and may include bags, filters and tubing. Plastic materials that make up the critical

**Table 4** Commonly Used Plastics in Disposable Systems

|                 |                                        |
|-----------------|----------------------------------------|
| Disposable bags | Polyethylene, ethylvinyl acetate, PVDF |
| Filters         | PTFE, polypropylene, PVDF              |
| Tubing          | Silicone, PTFE, PVDF                   |

*Abbreviations:* PVDF, polyvinylidene fluoride; PTFE, polyethylene tetrafluoroethylene.

components of a disposable system include filters (e.g., Millipore, Sartorius, Pall, GE Healthcare), tubing (e.g., Amesil, Saint Gobain), and disposable bags (e.g., Hyclone, Stedim, TCTech, Pall). Disposable bags are larger volume containers that are used for large volumes of drug substances or products and have the greatest dwell time of product exposure. These bags are used in upstream and downstream bioprocessing and in fill/finish operations, examples include media preparation, bioreactor, storage and transportation. Multilayer bags are typically used and are intended to maintain product integrity. These bags provide gas and moisture barrier properties, functionality after sterilization, durability and biocompatibility (Table 4). Very few materials possess a balance of properties in one layer and PVDF film may be the best solution (47). The outer layer of a multilayer bag provides durability, and many materials are used with varying thickness. These materials are made up of nylon, polyesters, ethylvinyl acetate (EVA) and polyethylenes. As a sandwich layer, ethylvinyl alcohol (EVOH) is commonly used. EVOH has extremely low gas permeation and excellent barrier characteristics. Because it has a propensity to absorb moisture and lose its barrier property, it is sandwiched in a multilayer bag. LDPE is commonly used as the drug contact layer because of its good chemical compatibility profile. While EVA films are typically considered superior as the product contact layer, there are limitations to large-scale manufacturing of EVA film, and, consequently, LDPE becomes a good alternative, especially with three-dimensional bags such as those used in disposable mixing applications.

Many factors are usually considered during the design phase when choosing a disposable bag. Two important questions to be addressed are: Is the plastic polymer safe and is it compatible with the solution it is in contact with? Several facets related to the qualification and selection of a disposable container must be considered to address these questions. This includes a validation package from the vendor with information related to the materials of construction, sterility, USP plastic class VI data, extractables, heavy metals, particulates, pyrogens and cytotoxicity testing from the vendor. This information—in combination with knowledge of the drug substance or drug product processing that may include processing volumes, chemical stability, compatibility, number of campaigns, formulation components, processing conditions such as temperature, pressure and, most importantly, extractable and leachable considerations—can provide insights into the choice of disposable bag for bioprocessing. The primary considerations should include:

*Chemical resistance study:* Chemical compatibility studies should be conducted to evaluate the choice of a single-use container prior to its selection. The tests can include weight loss, clarity, visual inspection, drop test, tensile strength, thickness of the film and testing using various solvent systems including buffers, organic solvents or other components that may be intended for drug product development. For most aqueous formulations, the plastics (e.g., LDPE, HDPE, PP, etc.) have an acceptable compatibility profile. However, organic solvent usage may cause incompatibility issues. Emerging disposable systems bags such as PVDF, which has a chemical compatibility profile similar to Teflon<sup>®</sup>, may offer options for accommodating formulations based on organic solvents.

*Protein adsorption:* Single-use systems are increasingly prevalent in downstream processing, final formulation development and in fill/finish of protein solutions. These systems gained acceptance for storage and processing at manufacturing scale of recombinant proteins and monoclonal antibodies in liquid or frozen forms. The

container-protein interactions may include protein adsorption onto the plastic container surfaces. The major driving forces influencing adsorption of protein are hydrophobic and electrostatic interactions. These interactions are responsible for nonspecific protein binding on a variety of surfaces. Interaction factors between plastic surface and protein could be affected by the physical nature of the surface (material surface or any coating), product formulation (pH, ionic strength, surfactant, etc.), storage conditions (temperature and contact time) and the concentration and conformational properties of the protein. Studies have shown a low binding level of model proteins on plastic polymeric surfaces compared with borosilicate glass surfaces. It is important to evaluate plastics using specific protein binding assays under various processing conditions, using large surface-to-volume ratios to determine their acceptability (53).

*Extractables and leachables:* The release of compounds from the plastic may affect product quality such as plasticizers, stabilizers or solvents. Regulations mandate that the equipment and materials used in the manufacture of pharmaceuticals should not alter the safety, efficacy and potency of the final drug product. An evaluation of potential extractables is required for plastic disposable bags to ensure compliance. Extractables are substances that can be extracted from a plastic using solvent or extraction conditions that are expected to be more aggressive than the processing conditions intended. Leachables are substances that could be present in the finished product because of interactions between plastics and the drug product during the products shelf-life. The suppliers of the plastic bags or components should provide a full and complete potential extractables list which could be used to evaluate product suitability with the plastic disposable bag (54).

*Sterile barrier integrity:* Maintaining integrity of a disposable device is critical to protect the product from microbial contamination. When plastic bags or components are provided as sterile, the integrity of these products must be demonstrated. Container closure validation can be performed to reduce the risk of compromise. These tests may include helium leak testing, pressure testing, dye ingress or microbial ingress challenges. Guidance documents from the FDA and European Medicines Agency (EMA) can help to define the level of validation and qualification necessary for the safety of the single-use systems. These include the FDA's guidance document issued in May 1999, "Container-Closure Systems for Packaging Human Drugs and Biologics" (45) and EMA's guidelines on plastic primary packaging materials (55).

## QUALITY AND REGULATORY CONSIDERATIONS

There are numerous plastic containers that have been used for parenteral applications, including drug products in cyclic olefin containers that have been approved for marketing in the United States, Europe and Japan (Table 3). Guidance documents from FDA and EMA help define requirements and the level of validation and qualification needed. This guidance has been universal to encompass all plastic containers for SVP or LVP, including vials, PFS or flexible bags. The FDA document "Container Closure Systems for Packaging Human Drugs and Biologics" provides the fundamental guidance on container closure systems, including plastic materials (45). The United States has a drug master file system (DMF) in which companies provide confidential information on the manufacturing and the composition of the plastic in a type III packaging material DMF and is incorporated into a letter of authorization for referencing the DMF upon FDA review. Canada has a similar DMF system, except that packaging materials are listed in a type II DMF. In Europe, the EMA limits the information contained in a DMF to drug substances; therefore, the drug manufacturer will usually provide the required information on the packaging system. Guidelines for plastic containers can be found in the newly revised EMA's Guideline on Plastic Primary Packaging (55). Both Ph.Eur. and USP have chapters referencing plastic materials and plastic packaging. Ph.Eur. section 3.1 has detailed chapters on various plastics including "polyolefins," and Ph.Eur. 3.2 specifically focuses on plastic containers (56,57). USP combines guidelines for plastic containers and plastic materials in chapter <661> (58). With respect to biocompatibility, both in vitro and in vivo

biological reactivity needs to be performed on plastic containers (59,60). The quality-conscious Japanese market has seen the plastic market grow significantly for SVP. Mitigation or elimination of particulates or defects, safety, break resistance and clarity are clearly the drivers for using plastics in Japan. Key JP guidance is described under General Tests Processes and Apparatus, 7.02 Test Methods for Plastic Containers and General Information 17, Plastic Containers for Pharmaceutical Products (61).

## SUMMARY

Application of plastics for parenteral delivery is expected to grow in years to come. Although PP material is more commonly used because of its availability and cost-effectiveness, there has been a recent surge in the use of superior plastics, the cyclic olefins, for parenteral delivery. The features of cyclic olefins are seen very favorable when packaging SVPs, highlighted by properties such as break resistance, glass-like transparency, better barrier properties compared with other plastics and its biocompatibility. However these features need to be balanced with the needs of a drug product, especially in the areas of oxygen or moisture sensitivities, where secondary packaging may help reduce such risks. Plastics are also favored because of their moldability and tight dimensional tolerance and can lead to newer design integrations. Examples include front finger grips, larger flanges and back stops for syringes. This capability is especially important because the home health care market is a growing segment. Many drug products are produced with the intention of being used in a home setting. Material flexibility also allows the same resin to be used in an assortment of designs, from vials through PFS systems, without substantial chemistry differences. Recently cyclic olefin syringes have become available in sterile assembled formats for ease of filling, similar to that of glass syringe packaging, making it easier for drug manufacturers to switch to plastics. Similarly sterile and nonsterile plastic vials and containers are also available.

Plastic container systems can also play a significant role in influencing the stability of a drug product. For example, they are used with drug products that would otherwise delaminate glass or with water-for-injection products to maintain pH. Recent advances in plastic PFS systems include developments in silicone-oil free and tungsten-free syringe systems that can help mitigate or eliminate any potential interaction of leachables from a packaging system. Formulators and package engineers now have more options to evaluate and optimize drug formulation with suitable packaging components at early stages of drug development. Protecting the drug product in a package that does not break or crack is a substantial benefit, especially with biological products that need low temperature storage and transport. Plastic vials are now considered in these areas. In addition, availability of plastic cartridges and plastic dual chambered syringe systems for liquid-liquid or lyophilized powder-liquid systems clearly illustrates the ability of vendors to offer such designs for various drug delivery applications. For large-volume packaging and processing of bulk drug products, plastic disposable bags are being considered. Clearly plastic disposable bags offer many benefits over stainless steel containers in downstream bioprocessing, including fill/finish operations; however, due diligence is a must for the right choice of plastic for the product. Plastics will increasingly be utilized throughout the entire total supply chain of pharmaceuticals and provide opportunities for total life cycle containment of pharmaceutical products. These opportunities can allow for the lowest total cost of ownership to be provided with plastic packaging materials.

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