Pharmaceutical Dosage Forms:
Parenteral Medications
Volume 1

Second Edition, Revised and Expanded

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Formulation of Small Volume Parenterals

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I. INTRODUCTION

Whereas a *parenteral* can be defined as a sterile drug, solution, or suspension that is packaged in a manner suitable for administration by hypodermic injection, either in the form prepared or following the addition of a suitable solvent or suspending agent [1], the term *small volume parenteral* (SVP) has been officially defined by the United States Pharmacopeia (USP) [2] as ". . . an injection that is packaged in containers labeled as containing 100 ml or less." The USP categorizes sterile preparations for parenteral use according to the physical state of the product as follows:

1. Solutions or emulsions of medicaments suitable for injection
2. Dry solids or liquid concentrates containing no additives which, upon the addition of suitable solvents, yield solutions conforming in all respects to requirements for injections
3. Preparations the same as described in class 2 but containing one or more additional substances
4. Suspensions of solids in a suitable medium which are not to be injected intravenously or into the spinal column
5. Dry solids which, upon the addition of suitable vehicles, become sterile suspensions

Although the term *sterile pharmaceuticals* is applicable to all injections (radiopharmaceuticals included), ophthalmic preparations, and irrigating solutions, this chapter emphasizes the formulation of injectable dosage forms.

The successful formulation of an injectable preparation requires a broad knowledge of physical, chemical, and biological principles as well as expertise in the application of these principles. Such knowledge and expertise are required to effect rational decisions regarding the selection of: (1) a suitable

vehicle (aqueous, nonaqueous, or cosolvent); (2) added substances (antimicrobial agents, antioxidants, buffers, chelating agents, and tonicity contributors); and (3) the appropriate container and container components. Inherent in the above decisions is the obligatory concern for product safety, effectiveness, stability, and reliability. This chapter focuses on the physica chemical aspects of preparing 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.

The majority of parenteral products are aqueous solutions, preferred because of their physiologic compatibility and versatility with regard to route of administration. However, cosolvents or nonaqueous substances are often required to effect solution or stability. Furthermore, the desired properties are sometimes attained through the use of a suspension or an emulsion. 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. An attempt will be made to cover some of the formulation approaches for proteins and peptides.

II. FORMULATION PRINCIPLES

A. 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 currently used for parenteral products.

One of the most important considerations in formulating a parenteral product is the appropriate volume into which the drug should be incorporated. The intravenous route is the only route by which large volumes (i.e., greater than 10 ml) can be administered, although the rate of administration must be carefully controlled. 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. Intravenous and intraspinal injections are generally restricted to dilute aqueous solutions, whereas oily solutions, cosolvent solutions, suspensions, and emulsions can be injected intramuscularly and 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 due to local effusion of tissue fluids. With intravenous 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 rheumatoidal 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.

B. Selection of the Vehicle

Most parenteral products are aqueous solutions. Chemically, the high dielectric constant 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, USP, is the solvent of choice for making parenterals. It must be prepared fresh by distillation or by reverse osmosis and contain no added substance. When it is not possible to use a wholly aqueous solution for physical or chemical reasons, 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

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 can occur as a result of changes in pH or temperature or by seeding from other ingredients or particulates in the solution. To enhance the solubility of drugs, in addition to using organic solvents that are miscible with water as cosolvents, other techniques can be employed. These include salt formation and prodrugs, which, although capable of greatly enhancing solubility, constitute new entities requiring additional clinical studies. Other substances used as solubilizers include the surface-active and complexing agents.

Surface-active agents, by virtue of their association tendencies in solution and the ability to orient into concentrated polar and nonpolar centers (micelles), have been used to solubilize drugs and other substances such as vitamins, hormones, sulfonamides, dyes, resins, and volatile oils. These surfactants are powerful wetting agents and form colloidal dispersions that have the appearance of a true solution.

Ethylenediamine is required in aminophylline injections to maintain the theophylline in solution since aminophylline is a salt that ionizes into its constituent ions theophylline and ethylenediamine.

$$\text{Aminophylline} \rightarrow 2\ \text{theophylline}^- + \text{ethylenediamine}^{2+}$$

Ethylenediamine, a strongly alkaline substance, is volatile and if it escapes, the pH will be lowered, causing theophylline ion to be converted to free theophylline ($pK_a \sim 8.8$), which is only slightly soluble in water (8 mg/ml).

$$\text{Theophylline}^- + H^+ \rightarrow \text{theophylline (free)}$$

Creatinine, niacinamide, and lecithin have been used for solubilizing steroids in the free alcohol form. The use of the salt or ester of these steroids or vitamins eliminates the need to use solubilizers but requires other additives to ensure stability.

A brief description of the phenomenon of solubility will be helpful to the formulator in selecting the best solvent or agent to overcome difficulties that arise in the preparation of pharmaceutical dosage forms containing poorly soluble drugs. With parenterals, the drug and other dissolved substances should remain solubilized throughout the shelf-life of the product.

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.

Table 1 Expressions for Approximate Solubility

Term	Relative amount of solvent to dissolve 1 part of solute
Very soluble	<1
Freely soluble	1-10
Soluble	10-30
Sparingly soluble	30-100
Slightly soluble	100-1000
Very slightly soluble	1000-10,000
Practically insoluble or insoluble	>10,000

Measuring Solubility. Methods for determining the solubility of drug substances in various solvents have been described [3-6]. The phase solubility technique is especially applicable to determining the solubility of pure substances and also detecting the presence of impurities [6]. In this method, successively larger portions of the substance are added to the same volume of solvent in suitable containers which are agitated at constant temperatures, generally 30 ± 0.1°C. In those containers in which excess drug is present (undissolved), samples of the supernatant are withdrawn and assayed until the concentration is constant (i.e., the system has reached equilibrium). For a pure compound, a phase solubility diagram is constructed as shown in Figure 1a. The solubility is readily determined by extrapolating the line with a slope of zero to the y axis. If an impurity exists in the substance, a phase solubility diagram as shown in Figure 1b results, which shows an inflection in the ascending line. Extrapolation of the horizontal line gives the solubility of the substance plus the impurity of the substance on the y-axis, while extrapolation of the ascending line gives the solubility of the impurity.

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 (van der Waals, London or Debye forces).

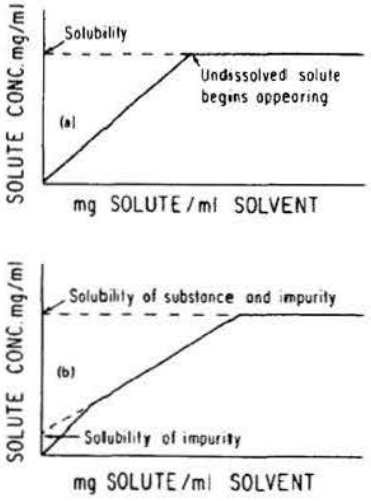


Figure 1 Phase solubility diagrams for a pure substance (a) and a substance containing an impurity (b).

The solubility of the drug substance is due in large part to the polarity of the solvent, often expressed in terms of dipole moment, which is related to the dielectric constant. Solvents with high dielectric constants dissolve ionic compounds and are water soluble, whereas solvents with low dielectric constants are not water soluble and do not dissolve ionic compounds. The former are classified as polar solvents (e.g., water, glycerin, and methanol), while the latter are nonpolar (e.g., chloroform, benzene, and the oils). Solvents with intermediate dielectric constants (e.g., acetone and butanol) are classified as semipolar. The dielectric constants of most pharmaceutical solvents are known [7,8] and values for a number of binary and tertiary blends have been reported [9] and, if not reported, can be readily estimated [10]. Table 2 is a listing of the dielectric constants of some liquids used in pharmaceutical systems.

The solubility profiles of a number of pharmaceuticals as a function of dielectric constant have been reported by Paruta and co-workers and others [11-17]. By determining the solubility of a substance in a system at various dielectric constants, a graph such as that shown in Figure 2 can be constructe to determine the dielectric constant that will provide the required solubility. As can be seen from the plot, to obtain the maximum concentration a dielectric constant of around 40 is required. Not all mixtures will show a maximum, but such a plot illustrates the required dielectric constant to obtain the desired concentration. For example, if a dielectric constant (d.c.) of 60 was selected, a mixture of water (d.c. 78.5), polyethylene glycol (PEG) 400

Table 2 Dielectric Constants of Some Solvents at 25°C

Solvent	Dielectric constant
Water[a]	78.5
Glycerin[a]	40.1
N,N-Dimethylacetamide[a]	37.8
Propylene glycol[a]	32.01 (30°)
Methanol	31.5
Ethanol[a]	24.3
N-Propanol	20.1
Acetone	19.1
Benzyl alcohol[a]	13.1
Polyethylene glycol 400[a]	12.5
Cottonseed oil[a]	3.0
Benzene	2.3
Dioxane	2.2

[a]Solvents used in parenterals

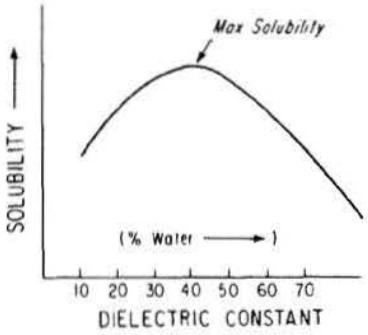


Figure 2 Hypothetical plot of solubility of a substance versus dielectric constant in various mixtures of dioxane and water.

(d.c. 12.5) and ethanol (d.c. 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 dielectric constant of 60 will have the following composition:

Ethanol	10%
PEG 500	16.5%
H_2O	73.5%

Since dielectric constant is a measure of the polarizability and dipole moment of a compound, several researchers have explored other parameters and polarity indexes [18] which are included by molecular volume, solvent and solute interactions, and specific interactions such as hydrogen bonding.

Hildebrand and Scott [3] introduced solubility parameters to predict solubility of regular solutions. Since pharmaceutical systems deviate from regular or ideal solutions, Martin and co-workers [19] 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 used by Amidon [20] and Yalkowsky [21] to predict solubility. These approaches were especially applicable to systems in which the intermolecular forces between solvent and solute were different. Figure 3 shows the solubility as a function of solvent concentration. The slope of the line is a measure of the activity in the solvent and was found to be related to several parameters of solubility including interfacial tension and hydrogen bonding [18,22].

Hydrogen bonding, the strongest type of dipole-dipole interaction, is characterized by a positive center in the hydrogen atom (proton donor). Because of its small size, the hydrogen atom 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.,

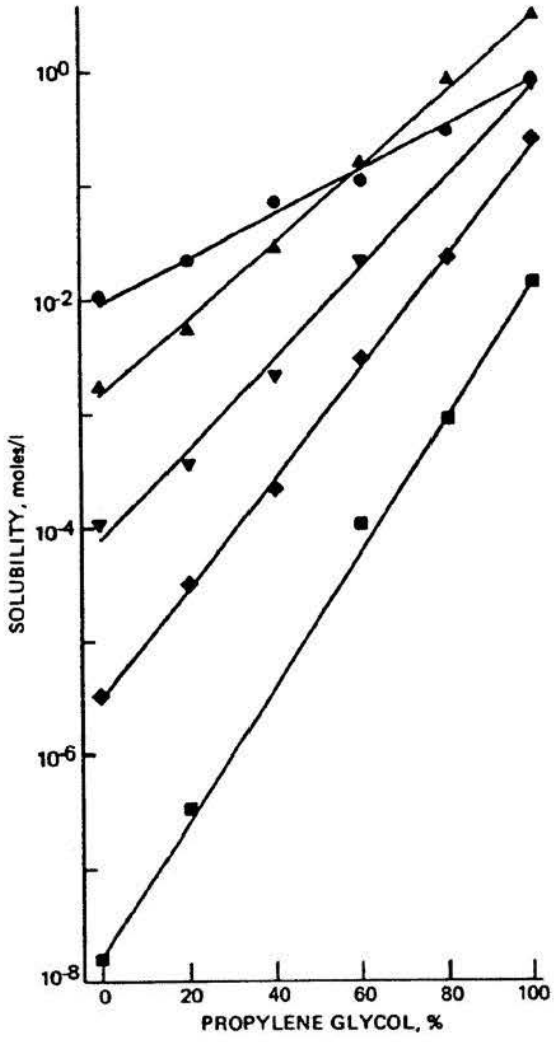
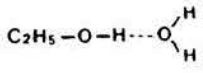
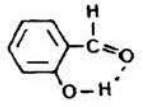


Figure 3 Log-linear solubility relationship for a series of alkyl *p*-aminoben: ates-glycol-water. [From Yalkowsky, S. H., Flynn, G. L., and Amidon, G L., *J. Pharm. Sci.*, *61*:983 (1972).]



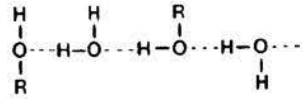
intermolecular H bonding

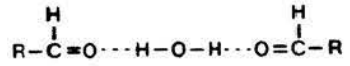


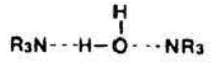
intramolecular H bonding

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.

Generally, the proton is donated by a carboxyl, hydroxyl, amine or amide group. The hydrogen from S—H or C—H can also form hydrogen bonds, but generally the bonds are weak. The proton attached to a halogen is generally quite active. HF forms strong hydrogen bonds. Typical electron contributors are oxygen, nitrogen and halogen atoms found in alcohol, ethers, aldehydes, ketones, amide and *N*-heterocyclic compounds. Some examples of hydrogen bonding with water follow:







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. Since the overall conformation of proteins is most influenced by hydrogen bonding, water—the solvent of choice for most proteins—contributes to the hydrogen bonding and, therefore, can have a strong influence on protein conformation.

Dipole-ion interactions are 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: (1) a high-dipole moment; (2) a small molecular size; and (3) a high dielectric constant 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 to the dipolar water molecules.

Generally, when electrolytes dissolve in water, heat is generated because the ion-dipole interaction energy exceeds the sum of the ion-ion interaction energy of the solute and the dipole-dipole interaction energy of the solvent. Examples of a negative heat of solution are anhydrous magnesium sulfate and sodium hydroxide. Where the ion-dipole energy is less than the sum of the energies holding the solute and solvent molecules together, heat is absorbed from the surrounding area to make up for the energy deficit. Electrolytes showing a positive heat of solution include potassium iodide and sodium bro-

mide. Hydrated salts generally show a positive heat of solution. Citric acid, sorbitol, and mannitol have positive heats of solution so that during dissolution the solution becomes cool. When reconstituting dry products containing large amounts of these substances, which is quite common in freeze-dried products, it is necessary to be aware of this phenomenon and warm the solution prior to injection.

Many complexes result because of an ion-induced dipole interaction. For example, iodine is solubilized in a solution of potassium iodide in the following manner:

$$I_2 + K^+I^- \rightarrow K^+I_3^-$$

Although the iodine molecule is electrically neutral, a temporary polarity may result from electronic movements within the molecule. Such movements induce dipoles in neighboring molecules and are responsible for maintaining benzene and carbon tetrachloride in the liquid state. The iodide complex forms because the strong electrical field of the electrolyte in solution induces a dipole in the polarizable iodine molecule. Benzene is a neutral molecule that is readily polarizable and soluble in alcohol.

Symmetrical molecules, such as benzene and carbon tetrachloride, possess a zero dipole moment and are nonpolar. Solubility of such molecules or their existence in a liquid state is due to van der Waals forces. In the manner described earlier, an induction effect occurs in these electrically neutral molecules, and the molecules orient themselves with surrounding molecules so that negative and positive poles are together. Such orientation is referred to as resulting from induced dipole-induced dipole interactions. These very weak attractions are sometimes called London forces, because they were first described by London in 1930. They are responsible for dissolution of hydrophobic substances in nonpolar solvents (e.g., wax in carbon tetrachloride and paraffin in petroleum benzin). If the solute and solvent in nonpolar systems are similar in size and structure, they can be mixed without any appreciable heat of solution. If the heat of solution is zero, the solution is referred to as an ideal solution.

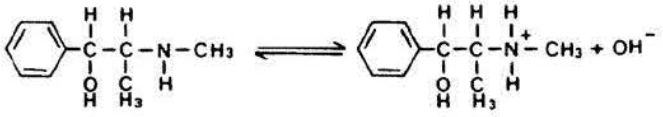
Another type of van der Waals force is that resulting from induced dipole-dipole interactions, also called Debye interactions. In this case, a dipolar molecule is capable of inducing an electrical dipole in a nonpolar molecule. A molecule that resonates, such as benzene, can be polarized by a dipolar substance such as methyl alcohol. Other examples of such interactions include mixtures of chloral hydrate in carbon tetrachloride and phenol in mineral oil.

Examples of drugs marketed in water-miscible systems include digitoxin, phenytoin, and diazepam. These injections are formulated in a water-miscible system containing glycols and alcohol and adjusted to a suitable pH. Other cosolvents used in parenterals include 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%. However, one product (Lorazepam) uses a complete cosolvent system, 80% propylene glycol and 20% polyethylene glycol; the latter two solvents have LD_{50} significantly higher than the other solvents mentioned, although tissue irritation has been implicated with all

the cosolvents when administered in high concentrations via the intramuscular and subcutaneous routes. Although such systems are stable in individual containers, care must be exercised upon 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 intravenous 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 [23]. The dielectric constant of 60, however, solvates the sodium salt by hydrogen bonding and van der Waals forces and reduces the risk of precipitations upon addition to an infusion solution prior to intravenous administration [24]. Nevertheless, such preparations should be administered slowly into the systemic circulation because rapid injection could result in the precipitation of the drug in the blood stream [25]. The influence of pH on solubility of phenytoin will be demonstrated later.

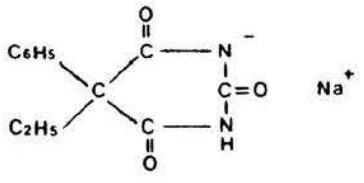
Effect of pH. Most drug substances are weak electrolytes and, therefore, exist in solution in the dissociated and undissociated forms. The ratio of these forms is determined by the pH of the solution. As a result, properties such as solubility, partition coefficient, and chemical stability, which are markedly different for the undissociated and dissociated forms, will be 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 due to 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.

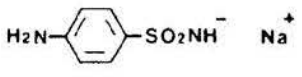


ephedrine cation in dilute acid

In compounds containing an electron withdrawing group, such as oxygen, a positive center is created, which in turn attracts electrons from an 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. This is illustrated for phenobarbital and sulfanilamide. The addition of acid to the solu-



phenobarbital anion



sulfanilamide anion

tions above will cause the free acid form to precipitate. Even the addition of a salt of a strong acid such as morphine sulfate will cause precipitation.

To calculate the solubility of a weak electrolyte as a function of pH, it is necessary to express the equilibrium in solution for a weak acid or weak base:

$$HA \overset{HOH}{\rightleftharpoons} H^+ + A^- \quad (1)$$

$$B \rightleftharpoons BH^+ + O\overline{H} \quad (2)$$

In Equation (1), (HA) represents the concentration of weak acid present in undissociated form at equilibrium, and (A^-) represents the concentration of dissociated (or salt) form present at equilibrium. In Equation (2), (B) is the slightly soluble undissociated basic substance and (BH^+) is the dissociated salt form. The concentration of the undissociated forms (HA) and (B) will remain essentially constant. Therefore, S_0, the solubility of the undissociated form, can represent the concentration of (HA) or (B) in solution. For a weak acid the dissociation constant K_a for the equilibrium between species may be written as

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

Rearranging yields

$$(A^-) = K_a \frac{(HA)}{(H^+)} \quad (4)$$

Total drug solubility, S, will be the sum of undissociated and dissociated forms.

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

or

$$S = S_0 + K_a \frac{S_0}{(H^+)} \quad (6)$$

Therefore, the total solubility of a weak acid electrolyte is a function of the hydrogen ion concentration. The solubility equation may be expressed in logarithmic form by rearrangement:

$$\log (S - S_0) = \log K_a + \log S_0 - \log (H^+) \quad (7)$$

or

$$pH = pK_a + \log \frac{S - S_0}{S_0} \quad (8)$$

Considering the earlier example, phenytoin, which is formulated as the sodium salt, the following equilibria occur:

$$Na^+ \text{ phenytoin}^- \overset{HOH}{\rightleftharpoons} Na^+ + \text{phenytoin}^- \quad (9)$$

$$\text{Phenytoin}^- + HOH \rightleftharpoons \text{phenytoin}_{(u)} + OH^- \quad (10)$$

These equilibria indicate that a high OH^- concentration is required in order to keep the reaction in the direction of the soluble dissociated species. The aqueous solubility of the undissociated phenytoin is 0.016 mg-ml^{-1} [26] and at pH values below 5, phenytoin exists essentially in the practically insoluble undissociated species. Using Equation (8), in which S_0 is the aqueous solubility of undissociated phenytoin and S is the total concentration of phenytoin in solution (i.e., phenytoin$^-$ and phenytoin$_{(u)}$), the pH required to maintain a concentration of 50 mg ml^{-1} in solution can be determined:

$$pH = 8.3 + \log \frac{1.823 \times 10^{-1} - 1.34 \times 10^{-5}}{1.34 \times 10^{-5}} \quad (11)$$

$$pH = 8.3 + \log 2874 = 11.7 \quad (12)$$

Therefore, in water for injection a pH of 11.7 is required. At this pH the phenytoin is 99.97% dissociated. In the commercial preparation the hydroalcoholic solvent maintains the solution at a lower pH due to the dielectric effect discussed earlier.

For a weak base the dissociation constant K_b for the equilibrium between species may be written as

$$K_b = \frac{(BH^+)(OH^-)}{(B)} \quad (13)$$

Rearranging yields

$$(BH^+) = K_b \frac{(B)}{(OH^-)} \quad (14)$$

The total solubility, S, is the sum of the dissociated and undissociated forms:

$$S = (BH^+) + (B) \quad (15)$$

or

$$S = S_0 + K_b \frac{S_0}{(OH^-)} \quad (16)$$

Since $K_w = (\overline{OH})(H^+)$, the hydroxyl ion concentration can be expressed in terms of the hydrogen ion concentration:

$$S = S_0 + S_0 \frac{K_b(H^+)}{K_w} \quad (1$$

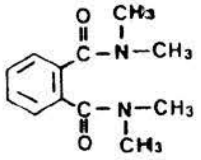
Expressed in logarithmic form,

$$\log (S - S_0) = \log S_0 + \log K_b + \log (H^+) - \log K_w \quad (2$$

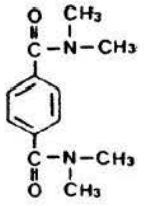
or

$$pH = pK_w - pK_b + \log \frac{S_0}{S - S_0} \quad (3$$

Effect of Molecular Structure. Spatial and structural relationships ofte play a major role in determining relative solubility. Crystals composed of unsymmetrical molecules tend to be more soluble than those of highly symmetrical molecules. For example, N,N,N^1,N^1-tetramethylorthophthalamide,

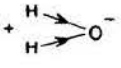


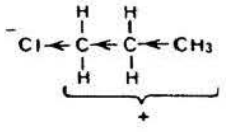
has a solubility of 700 g liter^{-1}, while the more symmetrical para form, is o



one-seventh as soluble. Symmetrical molecules tend to fit into the crystal lattice more readily than unsymmetrical molecules, which generally have hig er entropy factors (greater degree of disorder in orientation).

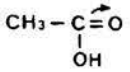
The tendency for atoms is to take on or discharge electrons from the ou shell in order to contain eight electrons, the most stable configuration. Th stabilization is achieved either by *induction*, which arises from an unequal sharing of electrons in a bond between atoms of different kinds or is transmitted through similar atoms, or by *resonance*, where polarization results in a net electronic displacement and the existence of an open or ionic bond. E amples of induction:





In propyl chloride the charge is transmitted through the chain to the electrophilic chlorine atom and therefore a negative charge rests with the chlorine while the positive charge is distributed over the carbon chain. Examples of resonance (electromeric shift):

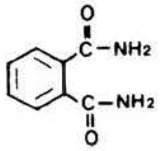
The above is often written



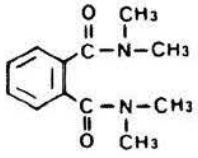
Inductive and electromeric shifts influence the strength of acids and bases by

1. Withdrawing electrons from the acidic group ($-CO_2H$ or $-OH$) and creating a positive charge on the acid group which then makes it easier for the H^+ to leave. *Note*: A shift of electrons to the acidic group would make it more difficult for the H^+ to leave.
2. Withdrawing electrons from a basic group ($-NR_2$), reducing basicity and causing a repelling of incoming protons. A shift of electrons toward the basic group will promote the attraction of protons.

The solubility of orthophthalamide,



is only 5 g liter^{-1} in water because of the strong dipolar nature of the amide function and the intramolecular bonding tendencies. Blocking these dipole-dipole interactions by substituting the hydrogens with methyl groups,



results in a 140-fold increase in solubility [27].

Often a substance will exist in more than one crystalline form, such as chloramphenicol, progesterone, sulfathiazole, cortisone, and prednisolone, to name a few. The polymorphs show different solubilities and rates of solution, hence different absorption (bioavailability) tendencies. Polymorphic transformations are structural differences resulting from different arrangements of molecules in the solid state. Polymorphism as it pertains to physical

and chemical stability and also to therapeutic activity has been discussed by a number of researchers [28-31].

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, ΔH, 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 the influence of temperature on solubility. The following equation shows the influence of temperature on solubility:

$$\frac{d \ln S}{dT} = \frac{\Delta H}{RT^2} \tag{20}$$

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 (20) can be written

$$\log S = \frac{\Delta H}{2.303R} \frac{1}{T} + \text{constant} \tag{21}$$

By plotting the logarithm of the solubility in moles per liter versus the reciprocal of the absolute temperature as shown in Figure 4, 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 negative value indicates that the process is

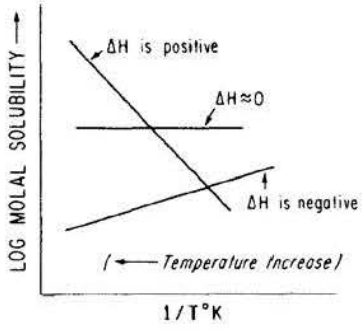


Figure 4 Effect of temperature on solubility of a substance. ΔH represents the differential heat of solution and is calculated from the slope of the line, $-\Delta H/(2.303)(1.987)$.

Table 3 Heats of Solution for Some Inorganic Compounds

Compound	H (kcal/mol)
Endothermic process	
Sodium sulfate, decahydrate	18.8
Silver chloride	15.0
Boric acid	10.8
Potassium iodide	5.1
Cesium chloride	5.0
Potassium chloride	4.2
Sodium chloride	1.0
Calcium sulfate, dihydrate	0.3
Exothermic process	
Sodium iodide	-1.2
Lithium chloride	-10.0
Calcium chloride	-17.4
Magnesium sulfate, anhydrous	-20.3
Aluminum chloride	-78.5

exothermic (i.e., the solute evolves heat when dissolving). In this case, an 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. The heats of solution for a number of substances are listed in Table 3.

Surfactants as Solubilizers. Drug solubility can be increased by the use of surface-active agents (surfactants) such as sorbitan monooleate and polyoxyethylene sorbitan monooleate. The surfactants are generally used in the range 0.05 to 0.5%.

They are effective solubilizing agents because by virtue of their wetting properties and association tendencies, they are able to disperse water-insoluble substances. These surfactants exist as individual molecules at low concentrations and can adsorb to the surfaces of molecules. At higher concentrations an orientated aggregation occurs and the surfactants exist as micelles. The concentration at which such association occurs is called *critical micelle concentration* (CMC). Surfactants can be either ionic (i.e., the ability to lower surface tension rests with the anion or cation in the molecule) or nonionic. Figure 5 illustrates the spherical orientations of nonionic and ionic micelles. It has been proposed [32] that poorly soluble hydrophobic molecules locate in the hydrocarbon core of the micelle, while polar molecules would associate with the polar ends. Molecules that contain polar and nonpolar gorups would 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. These mechanisms are schematically illustrated in Figure 6.

With the exception of the nonionic type, surfactants are not generally used in parenterals because of destruction to biological membranes. When such substances as well as the nonaqueous solvents are employed, it is essential that safety (LD_{50}, tissue tolerance, hemolysis, etc.) be evaluated.

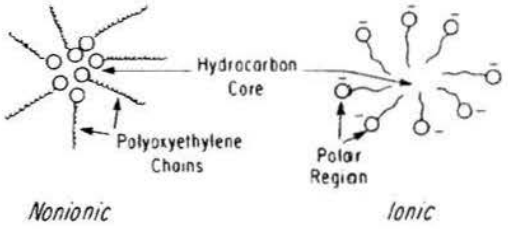


Figure 5 Diagrammatic illustration of the spherical orientation of surfactant micelles.

Cyclodextrins as Solubilizers. Cyclodextrins are oligomers of glucose produced by enzymatic degradation of starch. The number of α-1,4 linked glucose units determine the classification into alpha, beta, or gamma cyclodextrins having 6, 7, or 8 glucose units, respectively [33-36]. 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 [37]. The unsubstituted cyclodextrins are too toxic for parenteral use but the chemically modified cyclodextrins appear to be innocuous when administered parenterally.

2-Hydroxypropyl-β-cyclodextrin has been shown to effectively enhance the solubility of several steroids and proteins [38,39]. The solubility of alfaxalone, an insoluble anesthetic, was increased by 5000 times to 19 mg/ml in 20% hydroxypropyl-β-cyclodextrin [38]. The phase solubility curve is shown in Figure 7.

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 dielectric constant 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 [2] has monographs for Purified Water, Water for Injection (WFI), Sterile WFI, Bacteriostatic WFI, and Sterile Water for Irrigation.

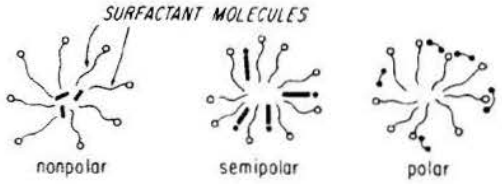


Figure 6 Schematic representation of the proposed mechanisms of micellar solubilization.

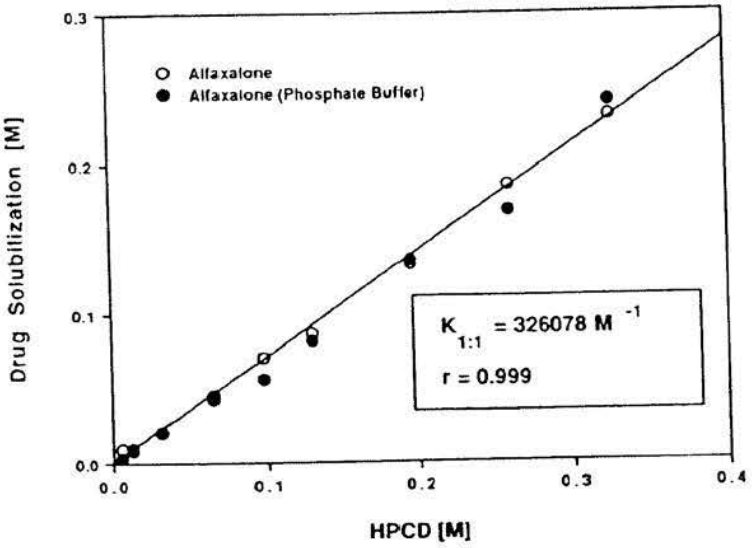


Figure 7 Phase-solubility of alfazalone in 2-hydroxypropyl-β-cyclodextrin (HPCD) in buffered or unbuffered media. The information presented in the boxed area refers to the unbuffered (O) system. (From Ref. 38.)

WFI is the solvent of choice for making parenterals. It must be prepared fresh and be pyrogen-free. Other USP requirements include no more than 10 parts per million (ppm) of total solids, a pH of 5.0 to 7.0, absence of chloride, sulfate, calcium, ammonium ions, and carbon dioxide, and limits for heavy metals and organic material (tannins, lignins). The tests required for WFI are generally the same among the various pharmacopeias but differences do exist with regards to limits. For example, only the British Pharmacopoeia and the USP have standards for particulate matter (standards not applicable to all parenteral dosage forms); only Pharmacopeé Belge has the same pH limits as the USP (5.0-7.0), other pharmacopeias are grouped at pH 6.8 to 8.4, or 4.2 to 7.6; several pharmacopeias limit only copper, lead, and iron, not heavy metals.

WFI may be prepared by either distillation or reverse osmosis but the distillation method is by far the most common and accepted method. Due to 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 and 85°C to inhibit microbial growth and prevent pyrogen formation. Generally, the water is continually circulated during storage and usually filtered again prior to use in manufacturing.

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 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).

Water Miscible. These cosolvents have already been discussed. Although water-miscible solvents are used in parenterals, principally to enhance drug solubility, it is important to mention that they also serve as stabilizers for those drugs that degrade by hydrolysis. Mixed-solvent systems may be irritating or increase toxicity, especially when present in large amounts or higher concentrations. A solution containing a high percentage of ethanol will produce pain on injection. It is also important to be aware that when such preparations are administered intravenously, too rapid an injection could result in the precipitation of the drug in the blood stream [25]. Excellent reviews of water-miscible solvents used in parenteral products have been published [16,17].

Nonaqueous. 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 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 [41]. Excessive unsaturation of an oil can produce tissue irritation. 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 4 summarizes the oil injections official in USP XXII.

C. Added Substances

Added substances such as antioxidants, buffers, bulking agents, chelating agents, antimicrobial agents, solubilizing agents, surfactants, and tonicity-adjusting agents must frequently be incorporated into parenteral formulas in order to provide safe, efficacious, and elegant parenteral dosage forms. Any additive to a formulation must be justified by a clear purpose and function. Hospital pharmacists who are involved in intravenous additive programs should be aware of the types of additives present in products that are being combined.

Pharmacopeias often specify the type and amount of additive substances that may be included in injectable products. These requirements often vary

Table 4 Official Injections in Oil

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

from compendia to compendia, so it is important to refer to the specific pharmacopeia that applies to the product in question. Two examples are sulfites and chelating agents. The USP allows the use of up to 3.2 mg of sodium bisulfite per ml of solution, whereas the French Pharmacopeia allows only 1.6 mg per ml.

Ethylenediaminetetraacetic acid derivatives and salts are sometimes used to complex and thereby inactivate trace metals that may catalyze oxidative degradation of drugs. Japan does not allow the use of these particular chelating agents in any parenteral product. Currently there are efforts to harmonize standards by the United States', European, and Japanese Pharmacopeias [42]. Table 5 lists the commonly used parenteral additives as well as their usual concentration.

Buffers

Changes in the pH of a preparation may occur during storage because of degradation reactions within the product, interaction with container components

Table 5 Commonly Used Additives in Parenteral Products

Substance	Usual concentrations (%)
Antimicrobial agents	
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
Antioxidants[a]	
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
Chelating agent	
Ethylenediaminetetraacetic acid salts	0.01-0.075
Buffers	
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
Tonicity adjustment	
Dextrose	4-5.5
Sodium chloride	0.5-0.9
Sodium sulfate[b]	1-1.6
Surfactants	
Polyoxyethylene sorbitan monooleate	0.1-0.5
Sorbitan monooleate	0.05-0.5

[a]Concentrations represent the maximum concentrations in parenterals.
[b]Do not use in glass containers containing barium [43].

(i.e., glass or rubber), and absorption or evolution of gases and vapors. To avoid these problems, buffers are added to many products to resist a change in pH. Excellent reviews on pH control within pharmaceutical systems by Flynn [44] and Kaus [45] 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. Above pH 9 tissue necrosis often occurs, while below pH 3, extreme pain and phlebitis are experienced. For intravenous SVPs the acceptable range is 3.0 to 10.5, because blood itself is an excellent buffer. Parenterals administered by other routes are generally adjusted to a pH between 4 and 9.

A suitable buffer system can be selected from knowledge of a 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. By following the degradation over a given pH range and plotting the rate constants versus pH, the pH of

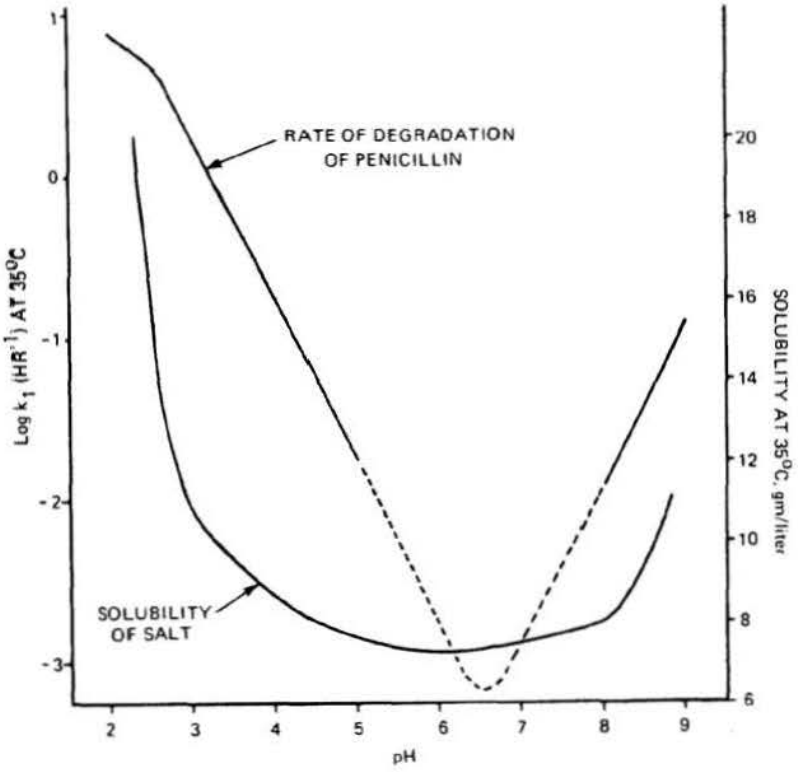


Figure 8 Solubility and rate of degradation of procaine penicillin G as a function of pH. [From M. A. Schwartz and F. H. Buckwalter, *J. Pharm. Sci.*, *51*:1119 (1962).]

maximum stability (pH 6.6) can be determined. In the case of procaine penicillin G, the solubility is lowest between 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, β, 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:

$$\beta = \frac{dB}{dpH} = 2.303C \frac{K_a H^+}{(K_a + H^{+2})} \tag{22}$$

where

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

A hypothetical plot of β 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 ±1.0 unit of the desired pH

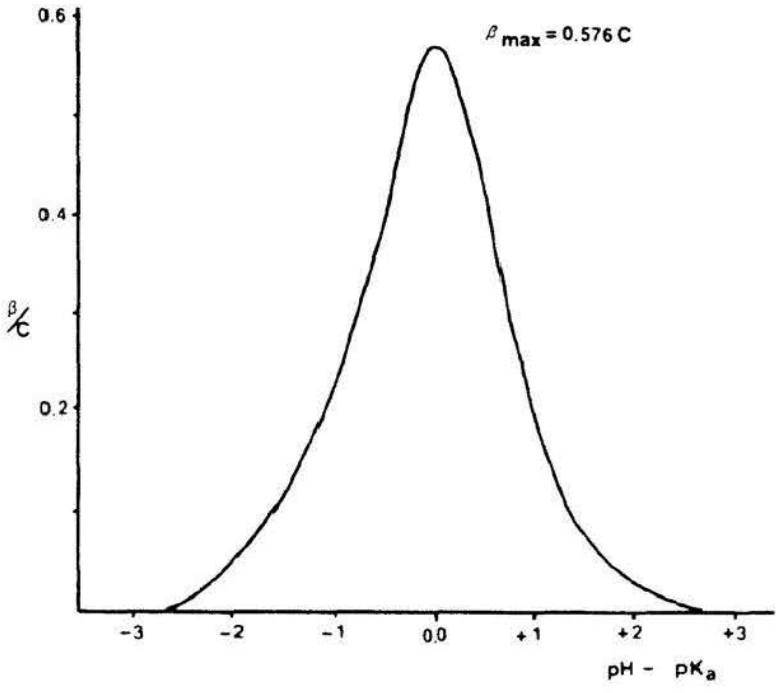


Figure 9 Theoretical buffer capacity curves of a monobasic acid.

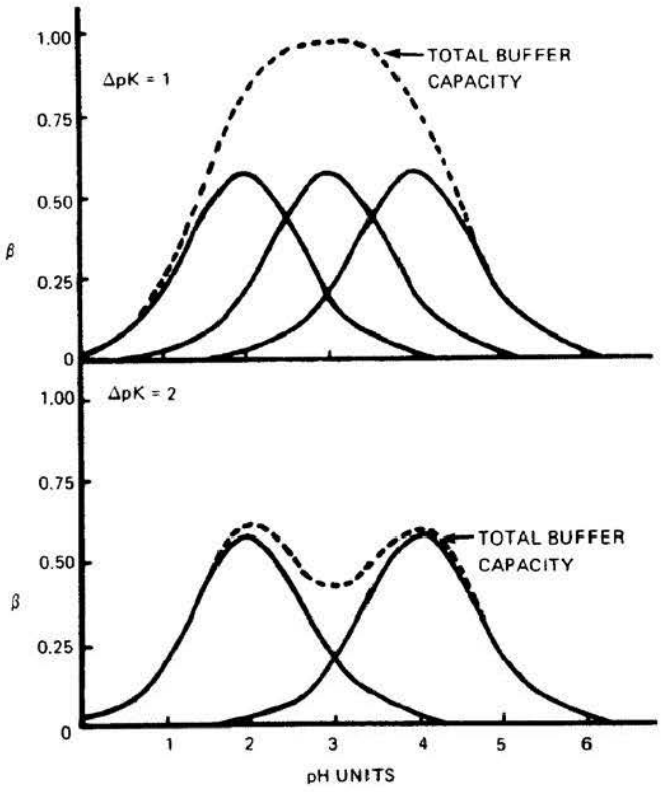


Figure 10 Hypothetical buffer capacity curves for polybasic acids. The total buffer capacity is represented by the dashed line. [From J. J. Windheuser, *Bull. Parenter. Drug Assoc.*, *17*:1 (1963).]

should be selected. For polyfunctional groups the buffer capacities of the individual species are additive (Fig. 10).

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. Buffer systems commonly used for injectable products are acetates, citrates, phosphates and glutamates. Figure 11 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.

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

$$pH = pK_a + \log \frac{C_{acid}}{C_{acid}} \qquad (23)$$

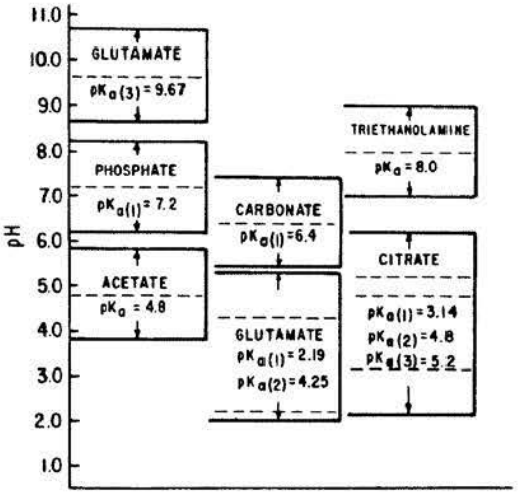


Figure 11 Effective range of pharmaceutical buffers, indicated by the arrows The dashed line represents the pK_a values.

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

$$pH = 4.8 + \log \frac{0.05}{0.1} \tag{24}$$

$$pH = 4.8 - 0.3 = 4.5 \tag{25}$$

The acetate system is suitable for the buffering of an injection of atropine sulfate. The pH of maximum stability is 4.0, while the maximum biological activity occurs at 6.8 to 7.2. Therefore, since it is desirable to have the solution easily adjusted to physiologic pH upon injection, as low a concentration of salt and acid as possible should be used.

Equation (23) shows that at equal molar concentrations of dissociated and undissociated species (i.e., $C_{salt} = C_{acid}$), the pH and pK_a are equal (point of maximum buffer capacity). The Henderson-Hasselbach expression is well suited for monobasic or univalent buffer systems such as acetate, diethanolamine, triethanolamine, and NH_4Cl and also for those polybasic systems where the pK_a values are sufficiently separated, such as for the phosphate and carbonate systems. However, for those systems where the buffer capacity curve overlap, such as the hypothetical illustration in Figure 10, and for example the citrate and glutamate systems (Fig. 11), all the species and pK_a values must be taken into account.

Although buffers assure the stability of pH of solution, the buffer system itself can alter other properties such as kinetic and solubility aspects. Buf-

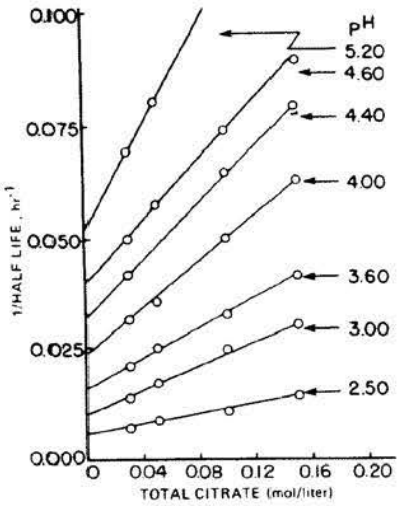


Figure 12 Effect of citrate buffer concentration on thiamine hydrolysis at 96.4°C at constant ionic strength and at different pH values. [From J. J. Windheuser and T. Higuchi, *J. Pharm. Sci.*, *51*: 354 (1962).]

fers can act as general acid or general base catalysts and cause degradation of the drug substance. Such a mechanism occurs with a number of amine and amine derivatives in systems containing polycarboxylic acids (e.g., citric, tartaric, and succinic). In such cases, as shown in Figure 12, the degradation of vitamin B_1 increases with increase in citrate buffer concentration. The degradation of chloramphenicol has been found to be pH independent below pH 7, but in the presence of buffers a pH rate profile as shown in Figure 13 occurs. The totally undissociated and ionized forms were found to be inactive, but the half-salt was highly unstable in the buffer systems.

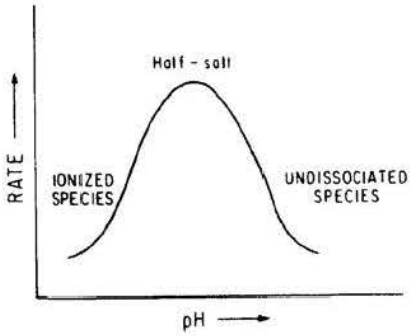


Figure 13 pH profile for the degradation of chloramphenicol in the presence of buffers showing that in the range where the species exists as the half-salt the degradation is buffer dependent.

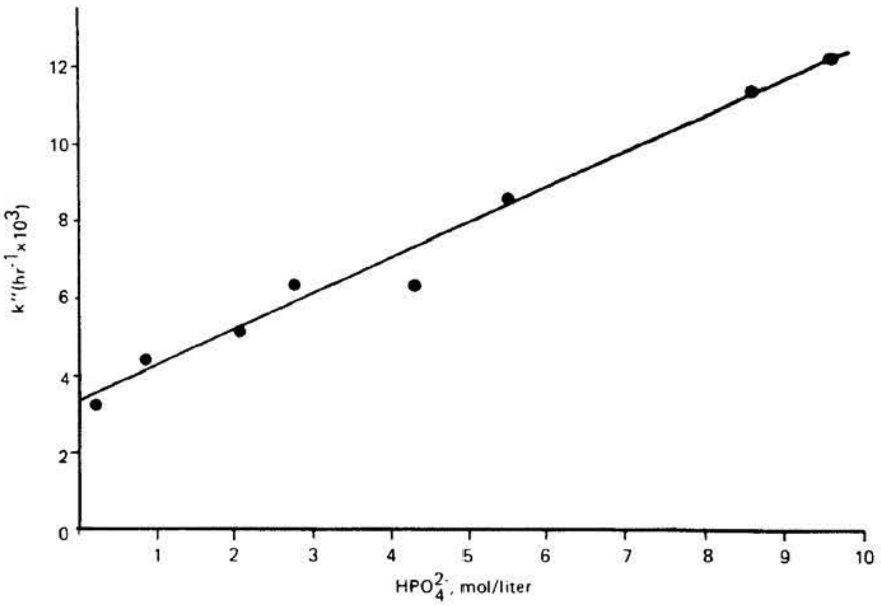


Figure 14 Catalytic effect of HPO_4^{2-} ion on the rate of hydrolysis of phenethicillin at 35°C. [From M. A. Schwartz, A. P. Granatek, and F. H. Buckwalter, *J. Pharm. Sci.*, *51*: 523 (1962).]

The ionic strength contributions of the buffer system can affect both isotonicity and stability. For example, if adjustment of pH is made with sodium hydroxide, say of a solution containing monosodium phosphate, the effect of the generation of disodium salt on isotonicity and the effect of HPO_4^{2-} ion on stability as shown in Figure 14 must be taken into account.

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. 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. By increasing the oxidation potential of the drug, oxidation can be minimized. As illustrated in Figure 15, lowering the pH of the solution will increase the oxidation potential. This occurs because according to a simplified version of the Nernst equation:

$$E = E^\circ + \frac{RT}{2} \log \frac{[H^+] \cdot [Ox]}{[Rd]} \qquad (26)$$

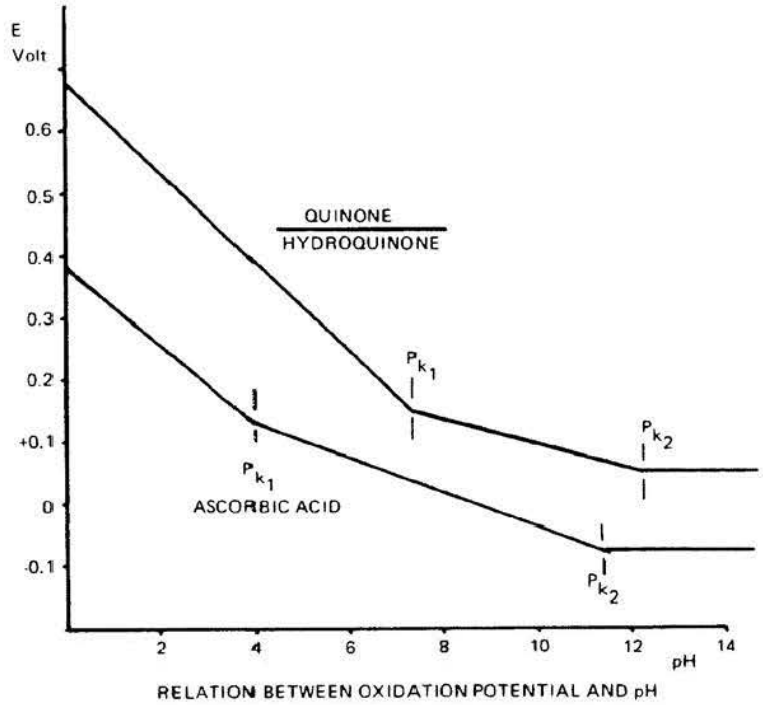


Figure 15 Relationship between oxidation potential and pH. [From G. Schell, *Farm. Rev.*, *58*: 45 (1959).]

an increase in hydrogen ion concentration causes an increase in the actual oxidation potential, **E**. In this equation E° is the standard oxidation potential, R the gas constant, T the absolute temperature, and 2 represents the number of electrons taking part in the oxidation-reduction reaction. For products in which oxygen is directly involved in the degradation (i.e., autooxidation), 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.

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: (1) by being preferentially oxidized and thereby gradually consumed or (2) 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 shown in Figure 16. However, above pH 5 the oxidation increases with increase in pH [46]. 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.

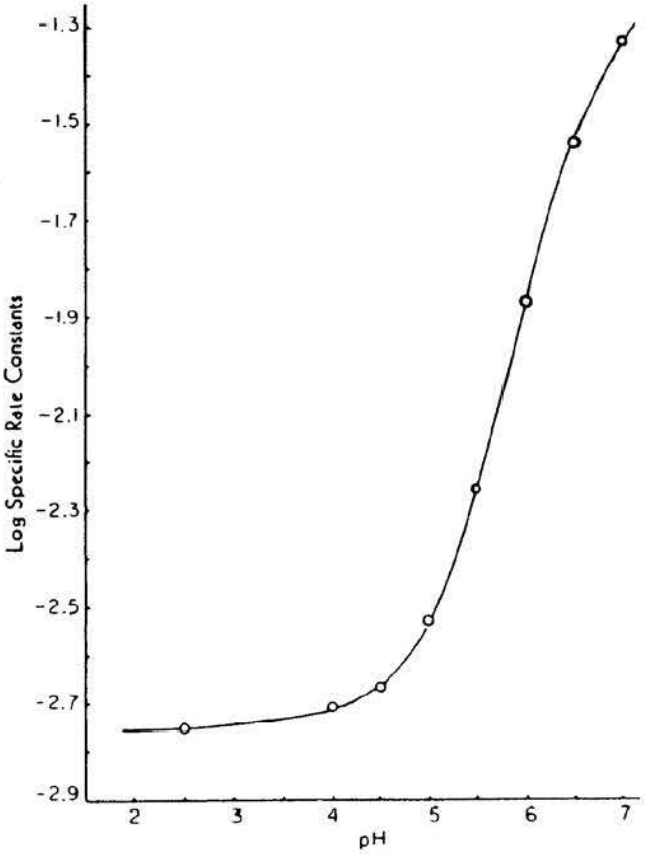


Figure 16 Reaction rate constant for the first-order oxidative degradation of morphine at 95°C as a function of pH. (From Ref. 46.)

In fact, ascorbic acid can act as an antioxidant for hydroquinone because it has a lower oxidation potential and will be preferentially oxidized. Table 6 lists some standard oxidation 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 this compound and the final pH of the formulation [48]. The metabisulfite is used at low pH values [49]. Some drugs can be inactivated by bisulfites. For example, epinephrine is stabilized through the formation of an addition product, epinephrine sulfonate, which is inactive [50]. Ortho- or para-hydroxybenzyl alcohol derivatives 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 [43]. Therefore, additional

Table 6 Standard Oxidation Potentials for Various Substances

Substance	E°[a] (V)	pH	Temp. (°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	+0.003	7.0	25
	-0.115	5.2	30
	-0.136	4.58	30
Methylene blue	-0.011	7.0	30
Sodium metabisulfite	-0.114	7.0	25
Sodium bisulfite	-0.117	7.0	25
Propyl gallate	-0.199	7.0	25
Acetylcysteine	-0.293	7.0	25
Vitamin K	-0.363	—	20
Epinephrine	-0.380	7.0	30
Hydroquinone	-0.673	—	—
Resorcinol	-1.043	—	—
Phenol	-1.098	—	—

[a] E° values correspond to the reaction (reduced) = (oxidized) + e^-.

Source: Ref. 47.

care must be exercised to inspect visibly 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 versus rubber stopper), single- or multiple-dose use, container headspace, and the expiration dating period to be employed.

Glutathione, an election donor, stabilized the photooxidation of menadione, a synthetic analogue of Vitamin K by a charge transfer complex formation [51], thereby blocking the light-catalyzed oxidative chain reaction. The photostabilizing effect of glutathione on menadione is shown in Figure 17.

Often a single antioxidant may not be sufficient to protect the product completely. Certain compounds (e.g., ascorbic acid and citric acid) have been found to act as synergists, increasing the effectiveness of antioxidants, particularly those that block oxidative reactions. Frequently, chelating agents such as ethylenediaminetetraacetic acid derivatives and salts complex with trace amounts of heavy metals which otherwise would catalyze oxidative reactions.

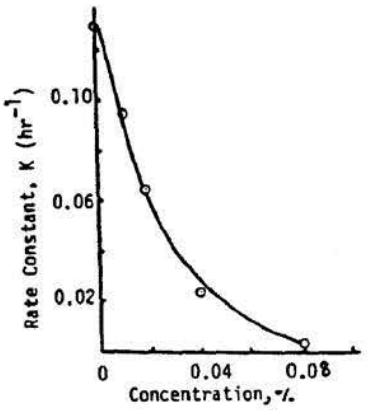


Figure 17 Effect of GSH concentration on the degradation rate constant of menadione sodium bisulfite (0.001%) in phosphate buffer at pH 7 under artificial sunlight at 30°C. (From Ref. 51.)

Antimicrobials

Agents with antimicrobial activity must be added to preparations packaged in multiple-dose containers unless prohibited by the monograph or unless the drug itself is bacteriostatic (an example being methohexital sodium for injection). They are often added to unit-dose solutions which are not sterilized at the terminal stage of their manufacture. In the case of multiple-dose preparations the antimicrobial agent is required as a bacteriostat to inhibit any microbes accidentally introduced while withdrawing doses. Antimicrobial agent may also serve a role as adjuncts in aseptic processing of products (e.g., syringes), where there may be product exposure during transfer, filling, and stoppering operations. Thus, should trace contamination occur during the manufacturing process, the antimicrobial agent may render the product sterile Also, antimicrobial agents should be present as adjuncts in intermittent heat sterilizations (i.e., tyndallization methods in which the product is subjected to two or more heat treatments at temperatures below that normally used for sterilization). Clearly, the use of antimicrobial agents is not a substitute for good manufacturing practices.

The most common antimicrobial agents are listed in Table 5. They fall into five basic classes of chemicals: the quaternary ammonium compounds, alcohols, esters, mercurials, and acids. The quaternary compounds are incompatible with negatively charged ions and proteins. They are most often used in ophthalmic products. The alcohols and esters are generally employed in parenteral products.

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.

Consideration must be given to the stability and effectiveness of the antimicrobial agent in combination with the active ingredient and other added substances. Many papers have been published describing the incompatibilities or binding of preservatives with surfactants, pharmaceuticals, and rubber closures [51-56].

Antimicrobial activity was shown by Kostenbauder [55] to be significantly reduced in the presence of macromolecules due to binding. The activity of the antimicrobial agent was due to the concentration of the free form, as illustrated in Figure 18. These workers showed that in the presence of polysorbate 80, the concentration of free antimicrobial agent was reduced in relation

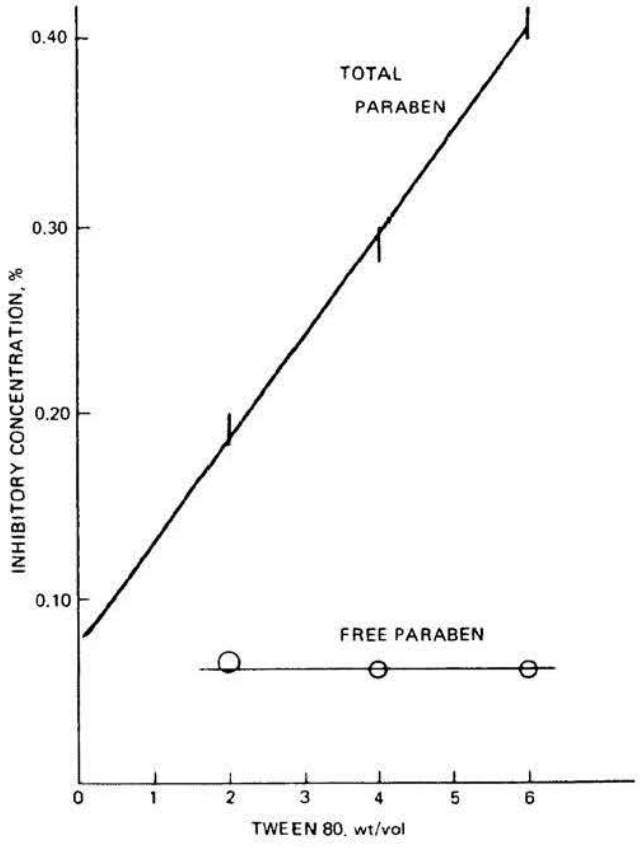


Figure 18 Comparison of the total methylparaben concentration and the free methylparaben concentration required to inhibit gorwth of *Aerobacter aerogenes* in the presence of polysorbate 80. [From F. Pisano and H. B. Kostenbauder, *J. Am. Pharm. Assoc. Sci. Ed.*, *48*:310 (1959).]

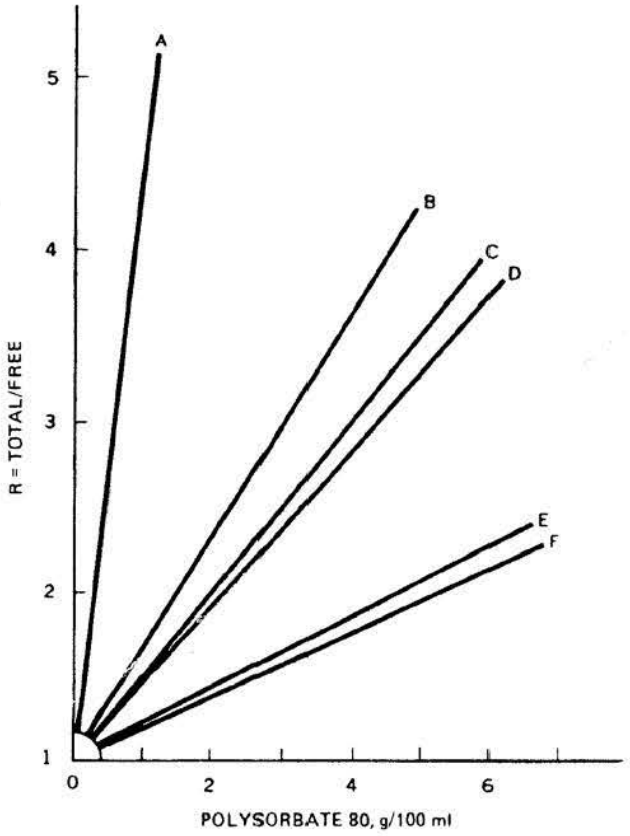


Figure 19 Binding of representative preservatives by a nonionic surface-active agent, polysorbate 80, in aqueous solution at 30°C. A = Propylparaben, B = methylparaben, C = chlorobutanol, D = benzoic acid, E = phenylethyl alcohol, F = benzyl alcohol. (From Ref. 55.)

to the nonionic surfactant concentration (Fig. 19). Such a plot follows the linear expression

$$\frac{\text{Total}}{\text{Free}} = 1 + kM \tag{27}$$

where k is the slope and M is the concentration of the macromolecule. Knowing the ratio of total to free preservative, the inhibitory concentration at any macromolecule concentration can be calculated from the following:

$$\frac{\text{Total}}{\text{Free}} \times \text{inhibitory preservative concentration at 0\% M} \tag{28}$$

Table 7 Influence of Nonionic Surfactant on Concentrations of Cationic Agent Required to Inhibit *Aerobacter aerogenes*

	Inhibitory concentration of	
Nonionic	Cetylpyridinium chloride	Benzalkonium chloride
0	1-100,000 to 1-250,000	No growth at 1-100,000
0.5% polysorbate 80	1-2500 to 1-5000	—
2.0% polysorbate 80	1-250 to 1-500	—
3.0% polysorbate 80	1-100 to 1-250	1-500 to 1-1000

Source: P. P. DeLuca and H. B. Kostenbauder, *J. Am. Pharm. Assoc. Sci. Ed.*, *49*:430 (1960).

Table 7 shows the concentrations of two quaternary ammonium compounds required to inhibit the growth of *Aerobacter aerogenes* in the presence of polysorbate 80.

Rubber closures and rubber extractives have been found to influence significantly preservative loss from solution and antimicrobial activity, respectively. Lachman and co-workers [54,56] 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. Table 8 shows the loss of these preservatives from solution in the presence of these rubber closures. On the other hand, the loss of preservative was minimal in the presence of butyl rubber.

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.

The effectiveness of antimicrobial agents can be tested by challenging the product with selected organisms to evaluate the bacteriostatic or bactericidal activity in a formulation. This challenge test described in USP [57] 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. Table 9 lists the minimum inhibitory concentrations (MIC) for a number of antimicrobial agents.

Tonicity

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 (erythrocytes) when introduced into hypotonic solutions will swell and often burst because of diffusion of water into the cell (hemolysis). If the cells are placed into hypertonic solutions, they may lose water

Table 8 Apparent Distribution of Preservative Between Rubber and Buffer Solutions[a] After 4 Weeks of Storage

Preservative	$Kt = \frac{Cr}{Cb}$ Closure	Temperature (°C) 25	40
Phenylethyl alcohol	Natural	1.72	1.39
	Neoprene	4.23	4.13
Chloro-β-phenylethyl alcohol	Natural	6.05	5.70
	Neoprene	16.40	21.80
Chlorobutanol	Natural	9.85	6.83
	Neoprene	14.50	14.50
Benzyl alcohol	Natural	0.63	0.63
	Neoprene	1.66	1.93
Methylparaben	Natural	1.36	1.43
	Neoprene	7.27	8.40

[a]Solutions buffered to a pH of 4.0.
Source: Ref. 56

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.

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. This is not always feasible, as a result of the high concentrations of drug utilized and the low volumes required for some injections, the wide variety of dose regimens and methods of administration, or product stability considerations. Historically, there has been concern over the osmolarity or tonicity of intravenous 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 parenteral dosage forms. The British Pharmacopeia [58] states that aqueous solutions for subcutaneous, intradermal, or intramuscular injection should be made isotonic if possible. As mentioned previously, sodium or potassium chloride and dextrose are commonly added to adjust hypotonic solutions. There are several methods available to calculate tonicity [59]. 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°C and is assigned a sodium chloride equivalent, E, of 1.00. The freezing point of blood (serum) is -0.52°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°C, the E value will be 0.1. Therefore, 1.0 g of the substance will be equivalent to 0.1 g of NaCl. To make 100 ml of a 1% solution

Table 9 Minimum Inhibitory Concentration (MIC) for Parenteral Antimicrobial Agents

Agent	MIC range[a] (%)	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, parasepts (methyl, ethyl, propyl, butyl esters)	0.05-0.25 methyl 0.005-0.03 others	0.18 0.02
Phenol	0.1-0.8	0.5
Phenylmercuric nitrate	0.001-0.05	0.002
Thimerosal	0.005-0.03	0.01

[a]Affected by product pH, ionic strength, storage temperature, packaging materials, etc.

of the substance isotonic, 0.8 g of sodium chloride must be added. A partial list of sodium chloride equivalents is shown in Table 10.

In the absence of a sodium chloride equivalent the L_{iso} method can be used. 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

$$E = 17 \frac{L_{iso}}{M} \tag{29}$$

where M is the molecular weight of the substance. Table 11 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.

As shown in Table 11 the L_{iso} for univalent electrolytes has a calculated value of 3.4. Therefore,

$$E = 17 \times \frac{3.4}{238} = \frac{57.8}{238} = 0.24 \text{ g-eq} \tag{30}$$

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

Table 10 Sodium Chloride Equivalents and Freezing Point Depression for 1% Solutions

Agent	Sodium chloride equivalent	Freezing point depression
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
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

Source: Partial list from *Remington's Pharmaceutical Sciences*, 17th Ed., 1985.

Table 11 Average L_{iso} Values

Compound type	L_{iso}	Example
Non electrolyte	1.9	Sucrose
Weak electrolyte	2.0	Phenobarbital
Divalent electrolyte	2.0	Zinc sulfate
Univalent electrolyte	3.4	Sodium chloride
Uni-divalent electrolyte	4.3	Sodium sulfate
Di-univalent electrolyte	4.8	Calcium chloride
Uni-trivalent electrolyte	5.2	Sodium phosphate
Tri-univalent electrolyte	6.0	Aluminum chloride

Source: *Remington's Pharmaceutical Sciences*, 17th Ed., 1985.

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 (Table 12). There is good agreement between measured and calculated values until the concentration becomes 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 semipermeable 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. 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,

Table 12 Comparison of Measured Osmolality Values with Those Calculated from Sodium Chloride Equivalents

Solution (g/100 ml)	Measured osmolality (mean mOsm ± S.D.)	Sodium chloride equivalent method	
		Osmolality (mOsm kg^{-1})	Percent of measured
Dextrose			
5.0	262 ± 5.9	249	95.0
10.0	547 ± 6.2	499	91.2
20.0	1176 ± 14.9	998	84.9
Alanine Glycine			
1.0 1.0	246 ± 0.5	256	104
2.0 2.0	480 ± 1.7	512	107
5.0 5.0	1245 ± 10.8	1281	103
0.2 NaCl in 5% dextrose	311 ± 5.85	312	100
0.45% NaCl in 5% dextrose	385 ± 5.48	390	98.7
Ringer's Solution, USP	294 ± 4.98	281	95.6
Lactated Ringer's, USP	264 ± 3.23	248	93.9
Travasol 5.5%	554 ± 11.4	596	107.6
67% Travasol (5.5%) 33% dextrose (50%)	1330 ± 29.6	1223	91.9

Source: Ref. 60

soreness, and tissue inflammation are often encountered in parenteral suspensions, especially those containing a high amount of solids.

D. 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. Because a delicate balance of variables is required in order 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 an 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. Injectable suspensions may be made with either vegetable oils or aqueous vehicles. Many contain low concentrations of solids (5% or less) whereas 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 aggregates into individual particles is called *deflocculation*. The size of individual particles may also change due to 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 bioavailability 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 in, and difference between the design of injectable suspensions and other suspensions have been summarized by several authors [61-64]. The requirements and limitations relate to: (1) microbiological purity; (2) ingredients allowed; and (3) mechanical flow properties. The microbiological purity requirements, like all parenterals, involve sterility and freedom from pyrogens.

There are 38 parenteral suspensions official in UPS XXII: 8 are oil based; the remainder are aqueous. 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, Insulin Zinc Suspension, USP, and Tetanus Toxoid Adsorbed, USP.

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, and perhaps a buffer or salt. Table 13 lists materials commonly used to formulate parenteral suspensions. Two basic methods are used to prepare parenteral suspensions: (1) sterile vehicle and powder are combined aseptically, or (2) sterile solutions combined and the crystals 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 μm 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 is obtained by aseptically filtering a solution of the drug through a sterilizing membrane into a 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

Table 13 Examples of Ingredients Used in Aqueous Parenteral Suspensions

Suspending agents
Aluminum monsterate
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

filtration. The sterile drug solution is added, aseptically, to the sterile vehicle, causing the drug to crystallize. The resulting suspension is then diluted with sterile vehicle, mixed, the crystals allowed to settle, and the supernatant solution siphoned off. The suspension is then brought to volume and filled in the normal manner.

Rheologically, an injectable suspension can present some formidable challenges. While a suspension can usually be formulated that can be filled, shipped, and injected, it is frequently difficult to formulate a product in which these three qualities will remain relatively unchanged throughout its shelf life [63]. 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 1-1/2 in. or longer needles, having internal diameters in the range of only 300 to 600 μm. 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. Syringeability includes characteristics such as ease of withdrawal from the container into the 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 re-

quired 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. Parenteral emulsions are rare because it is necessary (and difficult) to achieve stable droplets of less than 1 μm to prevent emboli in the blood vessels and it is not usually necessary to achieve an emulsion for drug administration. Formulation options are severely restricted through a very limited selection of stabilizers and emulsifiers primarily due to the dual constraints of autoclave sterilization and parenteral injection.

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)
3. Oil-in-water nutrient emulsions (given intravenously)

Dried Forms

Sterile solids are drugs or drug products packaged in a dry form which must be reconstituted or suspended in sterile vehicles prior to administration. Many drugs, particularly the cephalosporins and penicillins, are not sufficently stable in aqueous solutions to permit packaging them "ready to use." The pharmacist, nurse, and physician should be aware of the final form of a reconstitutable product. A dry solid may be intended to be reconstituted as a solution of as a suspension. If the final product is to be a solution, it should not be administered until all the solids are totally in solution. The key to the final product form can be distinguished from the title of the product.

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), will be 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 only 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 (USP).

Dry products which are to be reconstituted as suspensions by the addition of a suitable vehicle to yield a product meeing all requirements for sterile suspensions will be labled 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 described in sufficient detail elsewhere [65,

66], so only a brief discussion will be included. Freeze-drying, however, will be covered in more detail.

Powder Filling. This method involves filling sterile powder into indivdual containers under aseptic conditions in which a measured quantity, either on a weight or volume basis, is delivered to a wide-mouth container. 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 will 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 due to moisture in the powder.

Drugs that associate with water to produce crystalline forms are called hydrates. Water content of the hydrate forms of sodium cefazolin as a function of relative humidity is seen in Figure 20. As shown in the figure, the sesquihydrate is the most stable structure when exposed to extreme humidity conditions. This figure also reveals the importance of choosing the proper combination of hydrate and humidity conditions when designing a manufacturing process or facility.

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 filtration. Then 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, dried, and generally 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, and 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 procedure in a 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, 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 (see Fig. 21). 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 influencing 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.

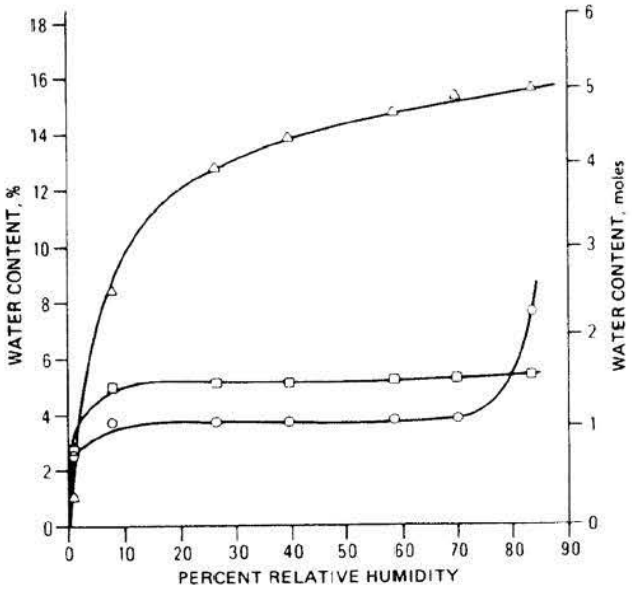


Figure 20 Relative humidity versus water content of hydrate forms of sodium cefazolin. -o-o-o-, Monohydrate; -□-□-□-, sesquihydrate; -△-△-△-, pentahydrate. (From Ref. 40.)

Freeze-Drying. From a historical standpoint the process of freeze-drying, often referred to as *lyophilization*, received its initial thrust during World War II when whole blood and blood plasma became lifesaving elements, and adequate supplies were jeopardized because of stability and shipping problems associated with these natural biological products. Soon after World War II, the pharmaceutical industry began considering the process for the preparation of sterile injectable dosage forms which could not be formulated into stable solutions. At the same time the food industry began employing freeze-drying to process and package foods, an application that continues to grow. Another application that has been receiving research attention is the preservation of biological substances, especially those of high worth or in short supply. Vital organs and tissues are also preserved by freeze-drying. Substances that degrade in solution become candidates for freeze-drying. This precludes storage of the product in a deep-frozen state which presents solubility problems, is costly, and there is always the risk of degradation. Often, freeze-drying offers the only means to stabilize the product or may be a convenient way to stockpile material for defense or emergency purposes and of course shipment and storage of dry material are less expensive than that in solution form. 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 ad-

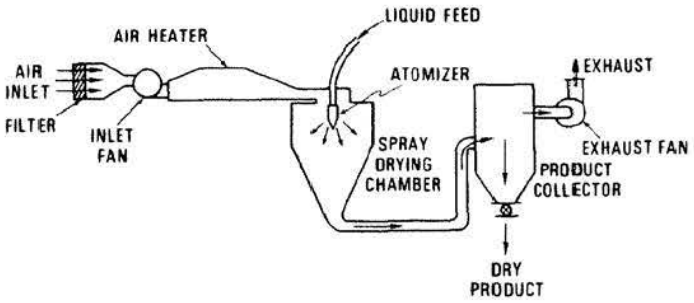


Figure 21 Schematic drawing of spray dryer.

vantage 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. Powder filling is used where the required dosage is represented by a large quantity of the drug or where the solubility is not adequate to freeze and as previously described with powder filling, sterilization of the powder is possible prior to filling.

The process of freeze-drying illustrated in Figure 22 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; (4) freezing the solution by placing the open containers on cooled shelves in a freeze-drying chamber or prefreezing in another chamber; and (5) applying a vacuum to the chamber and heating the shelves in order to sublime the water from the frozen state. 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., microorganisms, 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. The development of a suitable formulation and a freeze-dry cycle requires knowledge of some basic properties, such as: (1) eutectic temperature; (2) temperature effect on solubility; (3) thermal properties of the frozen solution; (4) degree of supercooling; (5) heat transfer properties of the freeze-dryer shelves, metal trays, glass vials, and the frozen product; and (6) equipment design and equipment capability. Formulating the solution to be freeze-dried must be done with a view toward the characteristics required at the time of reconstitution and administration. The drug alone often does not provide the solid content or characteristics appropriate for the finished product, and inert or relatively inert substances such as lactose or mannitol must be added prior to freeze-drying to provide the necessary bulk and desired characteristics.

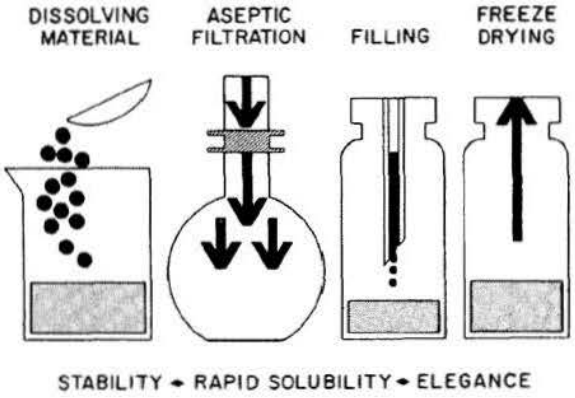


Figure 22 Freeze-drying process.

For a systematic approach to the development of a suitable freeze-dried product, knowledge of the various stages of the process is necessary. The main stages can be classified as freezing and drying. The initial freezing process is of critical importance since it will influence the pattern of the sublimation phase. The latter phase must occur from the solid state throughout the cycle. Appropriate cooling cycles must be determined 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 also affects the size of ice crystals. The slower the rate of freezing, the larger the ice crystals that form. Freezing of the solution is most conveniently accomplished in the chamber to be employed for drying, by placing the containers of solution on a shelf that is cooled by a circulating refrigerant, such as Freon, Cellusolve, or trichlorethylene. If the frozen system exhibits metastable or amorphous-glassy structures, these structures may need to be ruptured by appropriate thermal treatments (a succession of cooling and rewarming periods), thereby inducing crystallization of the amorphous material and adequate crystal size necessary for efficient sublimation.

The most commonly employed method of drying pharmaceuticals is condensation at low temperatures whereby, through the principal mode of conduction, heat is transferred to the frozen product to effect vaporization. By further introducing a cold surface into the system at a temperature below that of the frozen product, the water vapor evolved by the drying material will be condensed as ice on the refrigerated surface. The process is illustrated in Figure 23, together with the temperature gradient during the drying cycle. Factors influencing the rate of vaporization have been discussed extensively [67, 68]. The faster heat can be applied, the faster the drying proceeds, provided that (1) the temperature of the product remains below its liquefying point, and (2) a 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 until a phase separation occurs, resulting in the partial softening or puffing of the product.

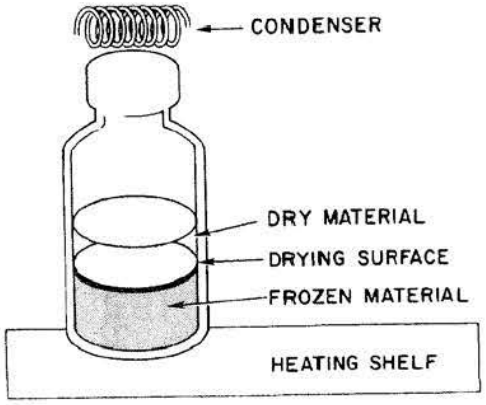


Figure 23 Drying process during freeze-drying. The temperature gradient is shelf > dry material > drying surface > frozen material > condenser.

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 pharmaceutical agents is of such magnitude that relatively small amounts are required for the lyophilized injectable dosage form. Therefore, the need for a 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 gelatin, mannitol, lactose, sucrose, dextran, sorbitol, mono- and dibasic sodium phosphate, calcium lactobionate, bovine serum albumin, and sodium chloride. It should be kept in mind when adding bulking agents that drying will be accelerated if the solute concentration is kept low.

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 and if the substance is vulnerable to collapse, a rigidizer such as glycine or mannitol may need to be added. Again it is important to point out that dilution is also a way to avoid meltback and collapse. So compromises and trade-offs are often necessary. If damage during freezing is a problem, a cryo-protective agent such as bovine serum albumin may be added or to minimize damage due to overdrying, sugars have been 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 cracking. 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.

Most freeze-dried drug products are oragnic electrolytes which exhibit eutectic points and supercooling tendencies. Several methods have been used for determining eutectic temperatures: (1) thermal analysis; (2) differential thermal analysis; and (3) electric resistivity. The electric resistivity method [69,70] involves the simultaneous monitoring of resistance and temperature of a frozen sample. Below the eutectic temperature the resistivity is very high, but when the eutectic is reached there will be a sudden change in resistivity due to a phase change and occurrence of liquid in the mass. An advantage of the resistance method is that not only can eutectic temperature be determined but the degree of supercooling and other phenomenon, such as recrystallization, can be assessed.

Examples of freezing and thawing curves are shown in Figure 24 for a 1.0 molar solution of an inorganic electrolyte, sodium chloride, together with the warming curve for pure water. For sodium chloride, the extent of supercooling is shown to be very significant with solidification occurring at about -30°C. In the event that the cooling curve was used to measure eutectic temperature, inaccurate information would be obtained as a result of the supercooling effect. The true eutectic temperature, as seen from the warming curve

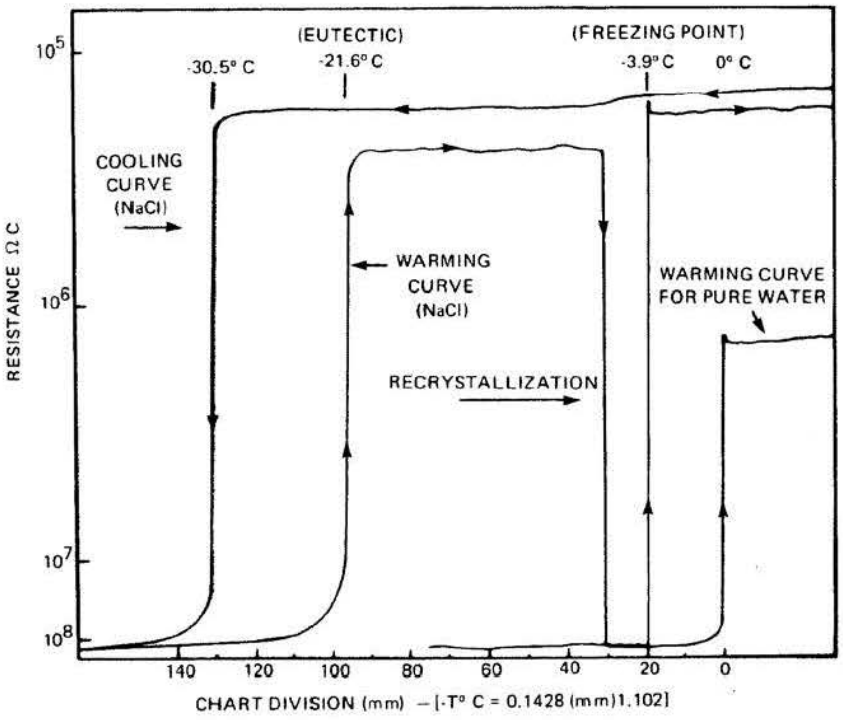


Figure 24 Resistance-temperature curves for the freezing and thawing of 1.0 M sodium chloride solution. [From P. P. DeLuca and L. Lachman, *J. Pharm. Sci.*, *54*:1412 (1965).]

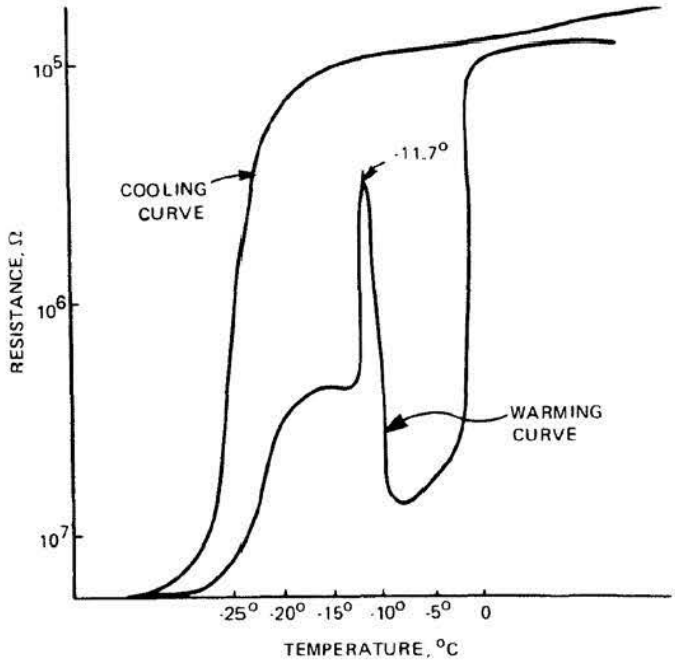


Figure 25 Cooling and warming curves for 0.3 M methylphenidate HCl solution. (From Ref. 69.)

in the figure, occurs at -21.6°C. The eutectic temperature is obtained fror the warming curve at the point where there is a sudden drop in resistivity or, conversely, an increase in conductivity, due to the occurrence of liquic in the cell containing the frozen mass. The curves shown in Figure 25 for organic pharmaceutical, methylphenidate hydrochloride, are somewhat more complex than those obtained for the inorganic electrolyte. Nevertheless, tl eutectic point (-11.7°C) can be determined from the sudden change in resis ity, indicating a phase transition.

A knowledge of the eutectic temperature of the additive is essential sin the addition of a salt such as sodium chloride to a drug with a eutectic sign cantly 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 sodium chloride and the phosphates, tend to form crusty-appearing cakes. This occurs during freezing and drying, probabl because of the phenomenon of recrystallization. Volatile substances are ger erally considered to be of little value to the finished cake but can be used i they accelerate the drying cycle. Dioxane, ethanol, t-butanol, dimethyl su oxide (DMSO), and acetone are examples.

Antimicrobial agents such as phenol, chlorobutanol, and benzyl alcohol serve only to preserve the solution prior to freeze-drying. One must remer ber that if a volatile substance is used for a temporary effect, complete rem al of the substance from the finished cake must be substantiated through ac

quate testing. The retention of volatile substances has been found to occur during the freeze-drying of liquid and semiliquid foods.

For compounds that do not form true eutectics, the variations of temperature in a freeze-dryer often result in a finished product of varying quality. Meltback, discoloration, and collapse are occurrences that necessitate rejection of all or parts of the batch. Quite often a substance is not considered to be a good candidate for freeze-drying and the process is discarded. Phase transitions that occur in the frozen state have been shown to influence the properties of the dried product [71]. Cefazolin sodium, commercially available as a freeze-dried product, freezes as the amorphous form and unless thermally treated to effect crystallization will remain in the less desirable amorphous state. Figure 26a is a thermogram obtained by differential scanning calorimetry for cefazolin sodium. The first endothermic shift occurs at -20°C (point B), an irreversible exotherm begins at -11°C (point C), and melting of ice begins at -4°C (point F). Considering the portion of the curve beginning just below the initial endotherm and to just above the irreversible exotherm, if warming were to proceed to just beyond the exotherm, say -6°C, and the system recooled to -25°C, upon rewarming, the dashed curve shown in Figure 26b, would result. This indicates that the frozen material has undergone transition. If, however, cefazolin was frozen and dried below -22°C (presumably the glass transition temperature), with no thermal treatment, the resulting product would be amorphous. This was confirmed using optical microscopy, scanning electron microscopy, and x-ray diffraction on freeze-dried material that was dried with and without thermal treatment. Material treated at -10°C exhibit birefrigence under crossed polars, defined shape by scanning electron microscopy (Fig. 27) and an x-ray diffraction pattern consisting of peaks of various intensity. All of these are indications of crystalline structure. Kinetic studies show that the crystallization can occur above -20°C (point B in Fig. 26b) and is very rapid above -11°C (point C).

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. Reconstitution is much easier, but there is the risk of introducing rubber particles. Butyl rubber is preferred over neoprene due to low moisture vapor transmission.

Temperature and pressure curves for a tpyical cycle are illustrated in Figure 28. With the circulating temperature set at 60°C, all the probed samples passed through 0°C within 6.5 hr. The heat was lowered gradually to 40°C and allowed to remain at this temperature until the run was terminated. From the temperature and pressure curves, it can be seen that maximum drying took place between 1 and 6 hr. The maximum vapor pressure difference between chamber and condensor occurred between 2 and 5 hr, with the chamber pressure reaching a minimum value of 15 μm after 10 hr. The leveling

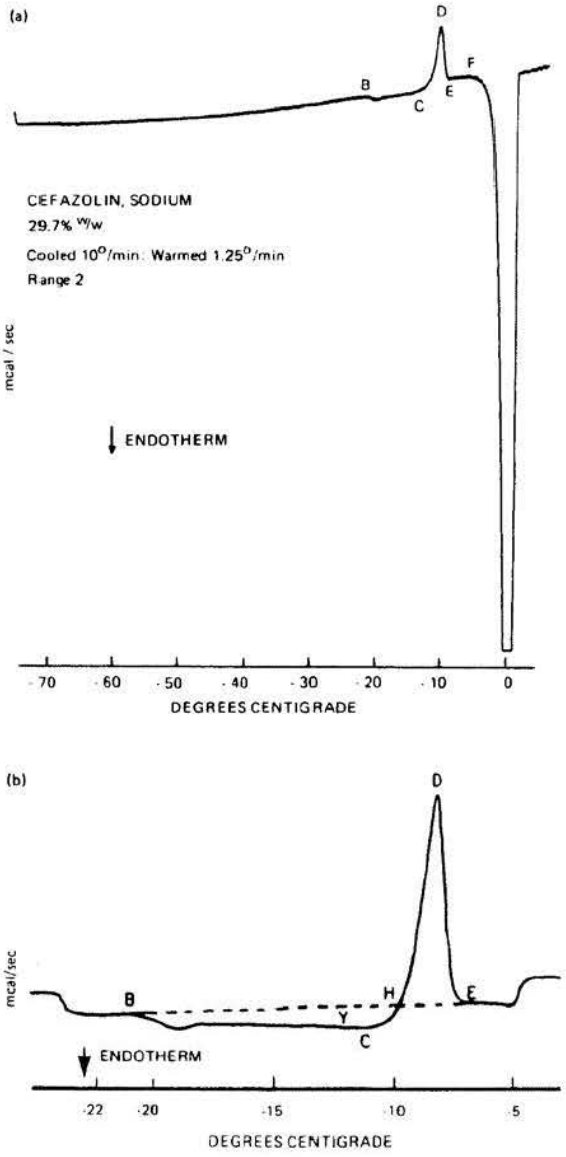


Figure 26 DSC thermogram for the warming of a frozen cefazolin sodium solution. (a) Temperature range between 0 and -70°C. (b) Endothermic and exothermic areas of the thermogram of cefazolin sodium. Solid curve corresponds to warming following freezing to -30°C; dashed line corresponds to the warming curve of the previous solution which was recooled after warming to -6°C. (From Ref. 71.)

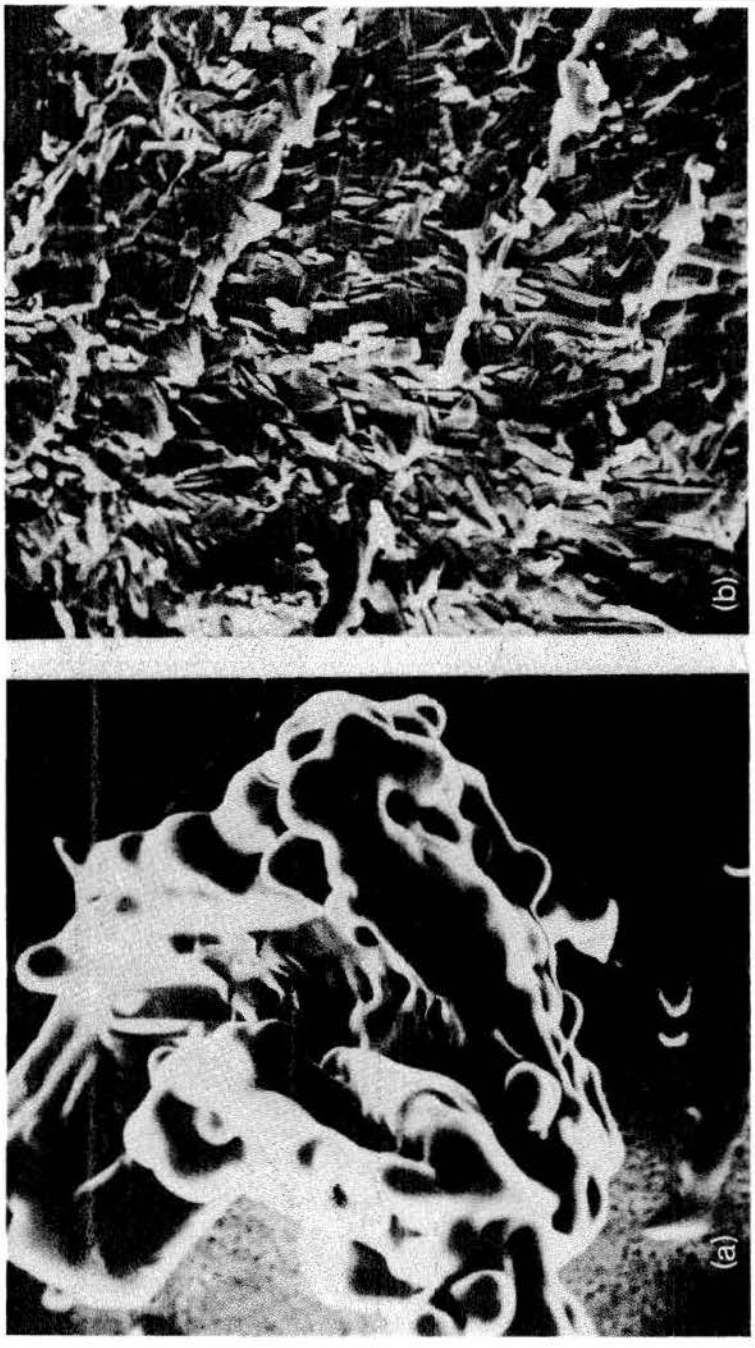


Figure 27 Scanning electron micrographs of freeze-dried cefazolin sodium. (a) Dried without thermal treatment. (b) Frozen mass warmed to -10°C and held 15 min before cooling and drying. Original magnification: 1200 × 10 kV. (From Ref. 71.)

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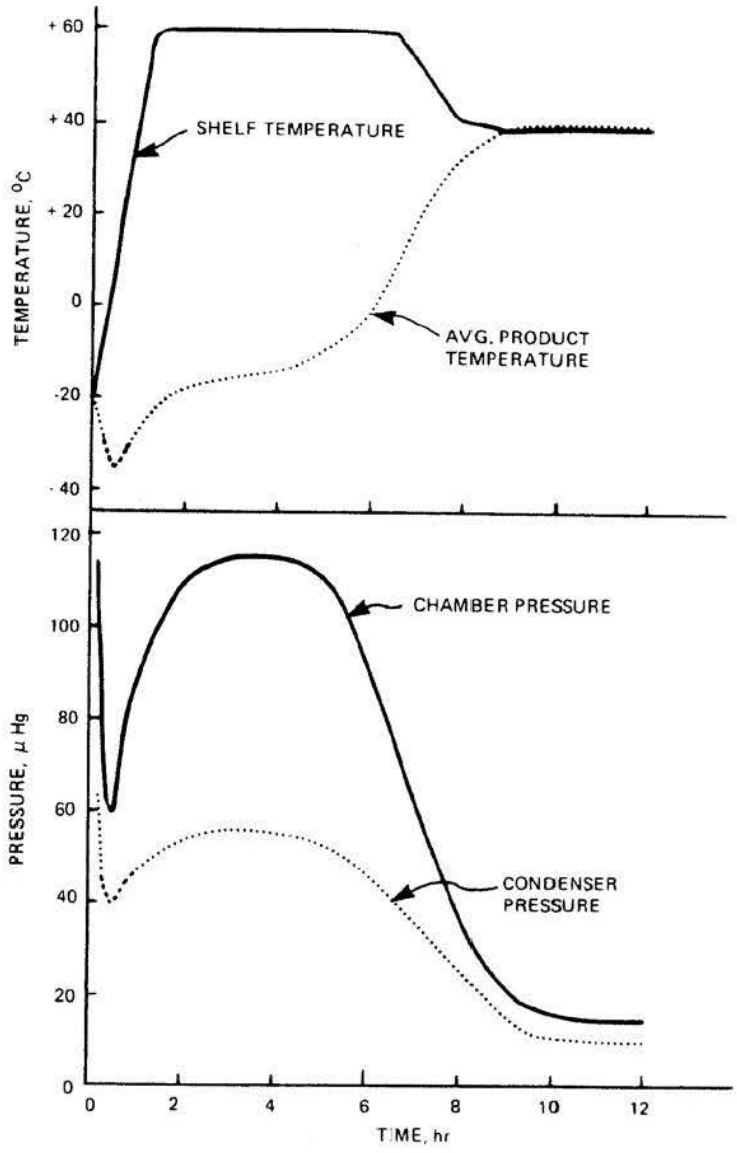

Figure 28 Temperature-time and pressure-time curves characteristic of the drying cycle for methylphenidate hydrochloride. [From P. P. DeLuca, *J. Pharm. Sci.*, *60*:778 (1971).]

off of the product temperature several degrees below the eutectic point (-11°C) during the primary drying phase was an indication that the heat applied was not excessive.

The application of freeze-drying to processing biological and diagnostic products has been growing. With this increased application, new problems are beginning to surface, such as the awareness that freeze-dried products can undergo structural and/or chemical modifications which might affect their physical properties, therapeutic effectiveness, and even their safety in clinical uses.

III. CONTAINER EFFECTS ON FORMULATION

Containers for parenteral products serve several purposes; facilitate manufacturing; maintain product protection, including sterility and freedom from pyrogens; allow inspection of the contents; permit shipping and storage; and provide convenient clinical use. The container components illustrated in Figures 29 and 30 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.

A. Glass

The three types of glass recognized by the USP for parenteral use are listed in Table 14. Type I is borosilicate and is the least reactive as measured by a

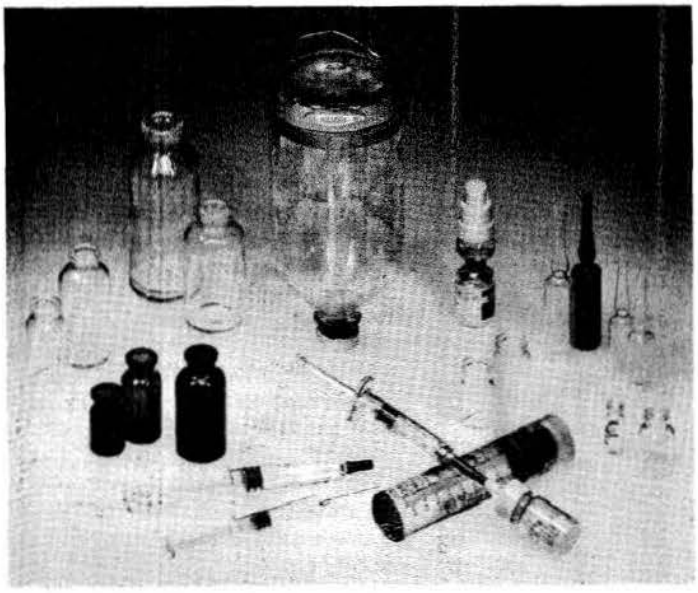

Figure 29 Representative parenteral containers.

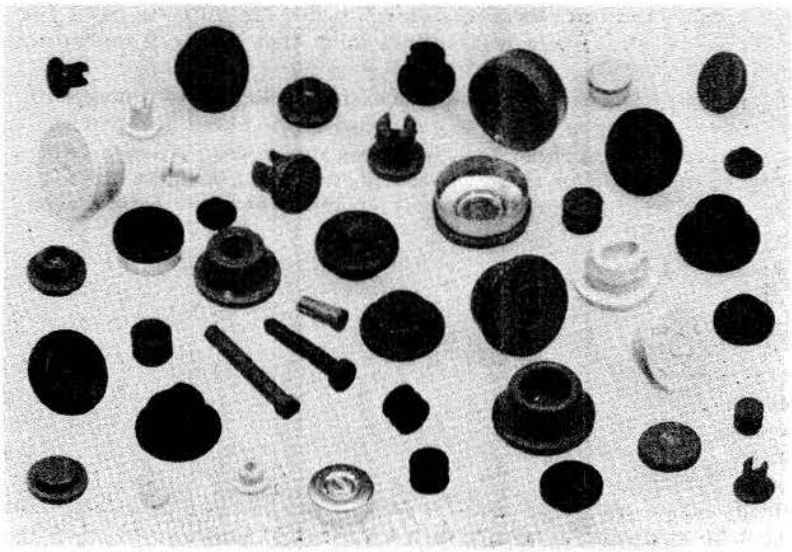

Figure 30 Representative parenteral closures.

standardized alkalinity test run on powdered (ground) samples. Types II and III glass are soda lime, with type II being surface treated with sulfate, sulfite, or sulfide to make it less reactive. Type I glass is, theoretically, the best all-purpose glass for injectables and should be the only glass that is used with alkaline products. However, it is significantly more expensive than types II and III. Type II glass is often used for solutions that remain below pH 7.0 during their shelf life, while type III glass can be used for dry powders that are reconstituted. The particular glass container intended for use must be an integral part of the product stability program to be described later.

Unfortunately, specifying the type of glass is not sufficient to ensure the consistency needed. Manufacturers have different recipes that bear designations, such as N-514A, CA-2, KG-33, and KG-35. Table 15 lists the compositions of various glasses. The glasses vary in additives—such as oxides of boron, sodium, potassium, calcium, iron, and magnesium—which alter physical and chemical properties of the glass. For example, when formulating sulfate salts (e.g., drug substances or antioxidant), the glass container should have minimal amounts of calcium and barium to prevent the formation of insoluble inorganic sulfates [43]. To meet this requirement KG-33 type I should be specified.

Amber glass containers are often used where the product is suspected of being light sensitive. The amber color is imparted by the addition of iron and manganese oxides, the cations of which are known to catalyze oxidative reactions. Studies have shown that these ions are extracted from glass [72] and that the decomposition rate of several drugs, thiomerosal [73], amitriptylene [74], and L-ascorbic acid [75] is enhanced in amber glass containers.

The Parenteral Drug Association has published guidelines on the processing and selection of glass containers [76]. Various surface treatments are

Table 14 Parenteral Glass Types and USP XX Test Limits

Type	General description[a]	Type of test	Limits: Size[b] (ml)	Limits: Milliliters 0.020 N acid
I	Highly resistant, borosilicate glass	Powdered glass	All	1.0
II	Treated soda-lime glass	Water attack	100 or less	0.7
			Over 100	0.2
III	Soda-lime glass	Powdered glass	All	8.5

[a]The description applies to containers of this type of glass usually available.
[b]Size indicates the overflow capacity of the container.
Source: USP XXII, p. 1571.

used to improve chemical resistance and decrease alkalinity. For example, exposing hot containers to sulfur dioxide reduces sodium content at the surface and a brief treatment with ammonium bifluoride effectively cleans the surface by dissolving a portion of it.

Containers should be washed in a clean area in which particulate and microbiological contamination is low. Containers are frequently shrink-wrapped with plastic to maintain low particle levels after they are manufactured and to reduce the amount of cardboard introduced into the parenteral manufacturing area. The washing of the glass must effectively clean the surface and remove particulates. The procedure consists of a rinse of deionized water, followed by a detergent wash and finally a thorough rinse with Water for Injection. If pyrogen-free water is not used, the glass should be sterilized and depyrogenated by dry heat immediately after washing.

B. Rubber Closures

The following classification lists most of the polymers utilized as parenteral closures:

1. Unsaturated elastomers
   a. Polybutadiene
   b. Polychloroprene
   c. Polyisoprene—natural or synthetic
   d. Nitrile butadiene rubber
   e. Styrene butadiene rubber
2. Saturated elastomers
   a. Copolymer of polyisobutylene and polyisoprene (butyl)
   b. Ethylene propylene rubber
   c. Ethylene propylene diene rubber
   d. Silicone rubber

Table 15 Representative Compositions[a] of Pharmaceutical Glass Containers

	USP classification/manufacturer's designations USP type I glass containers						
Chemical compositions	Kimble KG-33	Kimble KG-35	Kimble N51A	Wheaton NS-33	Wheaton NS-51	Wheaton NSV	Wheaton type I flint
SiO_2	80	69	71	81	73	73	70
B_2O_3	13	13	11	13	10	10	10
Al_2O_3	3	6	7	2	6	6	6
Fe_2O_3	0[b]	0	0	0	0	0	0
ZnO	0	0	0	0	0	0	0.5
TiO_2	0	0	0	0	0	0	0
MnO	0	0	0	0	0	0	0
BaO	0	2	2	0	2	2	2
CaO	0	1	1	0	1	0.5	1
MgO	0	0	0	0	0	0	0.5
Na_2O	4	8	6	4	6	7	9
K_2O	0	1	2	0	1	1	1

Chemical compositions	USP classification/manufacturer's designations						
	USP type I glass container			Type II and III glass containers			
	Wheaton type I amber	Kimble amber RN-3	Kimble amber 203	Kimble amber CA-2	Kimble R-6	Wheaton type III flint	Wheaton type III amber
SiO_2	66	67	69	73	68	72	73
B_2O_3	9	9	10	0	2	0.5	0.5
Al_2O_3	7	6	6	3	3	2	2
Fe_2O_3	1	1	1	0	0	0	0.2
ZnO	0.5	0	0	0	0	0	0
TiO_2	0	0	3	0	0	0	0
MnO	6	6	0	0	0	0	0
BaO	1	1	2	0	2	0	0
CaO	0.5	2	1	10	5	8	9
MgO	0	0	0	0	4	3	1
Na_2O	8	7	16	13	15	14	14
K_2O	1	1	2	1	1	0	0

[a] Approximate percentage compositions.
[b] A value of zero indicates that the material is not a component of the formulation; it may be present at trace levels. Type II and III containers differ only in surface treatment; their bulk composition is identical.
Source: Parenteral Drug Association, Glass Containers for Small Volume Parenteral Products: Factors for Selection and Test Methods for Identification, *Tech. Methods Bull. No. 3* (1982).

Rubber closures are formulated from many ingredients. The resultant products are exceedingly complex and difficult to characterize fully chemically. Ingredients used in addition to the basic polymer might include:

Accelerators: Amines, thiol and thiuram compounds, sulfamides, ureas
Activators: Stearic acid, zinc oxide, zinc stearate
Antioxidants: Amines, diethiocarbamates, paraffin waxes
Vulcanizing agents: Sulfur, organic peroxides, phenolic resins
Pigments: Carbon black, chromium oxide, iron oxide
Plasticizers and lubricants: (processing acids): Paraffin, mineral oils, fatty oils, organic phosphates, phthalates
Reinforcing agents (fillers): Aluminum and calcium silicates, titanium dioxide, carbon black, silica, barium sulfate

The elastomer and additives are combined by kneading them into a homogeneous mass, which is then vulcanized into the desired closure shape. During vulcanization heat is applied to the mixture. This causes a chemical curing of the formula into its permanent shape and properties. Production variations that may occur during the manufacture of stoppers can affect the quality and the properties of the stopper. To maintain batch-to-batch uniformity of a particular formulation, strict control of the manufacturing process is necessary. Ethylene propylene elastomers require very few additives compared to many of the others; thus they usually have less extractables.

The quantitative or qualitative formula of an elastomeric closure is rarely available to the drug product formulator. Rubber manufacturers do submit a master file to the Food and Drug Administration (FDA), including the quantitative composition of their closures. However, this information is regarded as confidential and therefore is not available from the FDA. This position is perhaps somewhat understandable for competitive reasons within the rubber industry, but this secrecy severely hampers the pharmaceutical chemist in evaluating formulas and conducting compatibility and stability studies. With better methods of analysis, the selection and control of elastomeric closures are beginning to be based on something more than empirical evaluation.

Physical Properties

Guidelines for the selection and processing of elastomeric closures have been proposed by the Parenteral Drug Association [77,78]. A number of physical properties have been identified as being important in the selection and control and should be understood by the formulator.

1. Compression set: Some rubbers deform permanently when held under pressure, thereby reducing the sealing characteristics of the closure with the glass vial. Natural rubber has the best resealing characteristics.
2. Coring: Coring occurs when a small plug or fragment of rubber is cut and dislodged from the stopper as the needle is inserted. The elastomer type, formulation, and closure design (including thickness of target area) and the needlepoint design all influence the coring rate.

3. Durometer: This is a measure of the hardness of rubber. In general, a value of 30 to 35 is soft, 35 to 45 average, and above 45 is hard. High durometer values usually mean increased resistance to puncturing. A high durometer value is needed for syringe plunger-heads.
4. Moisture vapor transmission (MVT): MVT is an important consideration when selecting a closure for hygroscopic powders, lyophilized products, and for products in which an inert gas is overlayed. MVT is inversely proportional to the thickness of the barrier. Generally, increasing the filler will decrease MVT. Butyl elastomers provide good MVT protection, whereas natural rubber is poor.
5. Puncture resistance: The pressure required to insert the needle through the closure is an important physical characteristic. Injections which are normally administered with small-diameter needles (23-25 gauge) must have lower puncture resistance than those administered with needles having a comparatively larger diameter (18-22 ga).
6. Resealability: Resealability will vary with rubber stocks. Since stoppers must reseal to prevent contamination and leakage, resealability is an important characteristic to evaluate.
7. Tackiness: For ease of handling, stoppers should not stick together or clump during processing. This usually occurs when stoppers are heated during sterilization.

Product Compatibility

Normally, if enough tests are run, a closure that is compatible with the parenteral product can be obtained by this empirical approach. The most common compatibility problem which occurs with stoppers is the leaching of ingredients from the stopper and the reaction of these ingredients with the product. Another problem is the sorption by the closure of preservatives, as described earlier, or other ingredients in solution resulting in subpotency or inadequate preservation. Due to the large variety of ingredients in most elastomeric formulations and chemical reactions they undergo, specific ingredients that might leach into the product, and possibly cause discoloration, turbidity, or precipitation, are often difficult to identify. Qualitative and quantitative determinations of ingredients from extracts of various stopper formulations, obtained under accelerated storage conditions, using various solvents, pH conditions, and so on, often provide the formulator with additional insight in selecting the proper elastomeric formulation for a product.

The USP XXII-NF XVII has a section on the biological and physical-chemical testing of plastic and rubber closures. The biological tests include acute systemic toxicity and intracutaneous reactivity tests. Other tests outlined include measurement of turbidity, reducing agents, heavy metals, total extractables, and pH.

Stoppers are normally prepared by washing them in household or commercial washers using detergents such as tetrasodium pyrophosphate or trisodium phosphate. In some cases a preextraction in an autoclave or with hot water may be required prior to detergent treatment to remove paraffin or surface wax. Gentle agitation with minimum tumbling should be used to avoid generation of particulate matter. Generally, an overflow process is employed to minimize agitation. Stoppers should be sterilized and dried immediately after wash-

ing. The sterilization cycle (autoclave) should be terminated with a vacuum cycle.

Special treatments of stoppers may include treatment with dilute acid or base solutions, solvent extractions, or extraction in a chelating agent to remove surface metals from the stoppers. An oxiglaze (oxidation) treatment is sometimes employed to create a slightly harder and slicker surface. This is normally done to facilitate automatic handling during packaging. The oxiglaze process is carried out by treating the stoppers with 5% sodium hypochlorite in diluted hydrochloric acid. Stoppers are generally coated with a thin film of silicone to facilitate handling or insertion into the vials. This is usually applied while tumbling the closures in a closed container in the presence of a carefully measured quantity of silicone.

A wide variety of injectable products and containers/closures as well as processing conditions can contribute to the presence of aluminum at different levels. Examples are salts containing phosphate, or glass vials, rubber closures, and autoclaving, which promotes extraction of aluminum from glass and rubber [79-81]. It has only been a recent finding that the accumulation of aluminum leads to clinically significant consequences [82]. Continuous intravenous therapy, particularly total parenteral nutrition was implicated in the inhibition of bone growth [83,84]. Although measures have been taken to minimize the problem of aluminum loading, it is unclear what the regulatory outcome will be for this issue that affects select, but key patient groups.

IV. STABILITY EVALUATION

A. Compendial and Regulatory Requirements

As internationalization of pharmaceuticals accelerates through corporate mergers and acquisitions, as well as political events—such as Europe 1991—it becomes increasingly necessary for the formulator to become familiar with and understand the regulations of the major industrial nations. Additionally, there is a concerted harmonization effort among four compendia: Europe, Great Britain, Japan, and the United States. Accordingly, this section gives an overview of current parenteral product stability regulations in Japan, Europe, and the United States.

Japan

The document *Requirements for the Registration of Drugs in Japan* [85] states that "the stability of bulk powders and finished products shall be studied under all possible conditions of handling." In addition, decomposition products should be identified and the toxicity and pharmacology evaluated, if necessary.

Storage tests are divided into three categories: long-term, severe, and accelerated. These are outlined below.

1. *Long term testing* is designed to answer the question, "Is quality maintained in a fixed period of distribution?" Two experimental approaches are allowed: namely, Methods A and B. In Method A, 3 lots are stored at room temperature (or the storage condition on the label, if different) for 3 years (or longer, if appropriate) and assayed at intervals not exceeding 6

months. In Method B, 3 lots are stored at 25 ± 1°C/75 ± 5% relative humidity (RH) for 2 years and assayed at intervals of 3, 6, 9, 12, 18, and 24 months.

2. *Severe testing* is intended to estimate stability at room temperature and investigate decomposition products. Included is an evaluation of the effect of temperature, RH, pH and light. Decomposition products are to be identified and major ones are to be tested for toxicity and pharmacology.

Recently, the Research and Technology Committees for Drug Standards organized by the Osaka Pharmaceutical Manufacturers Association and The Pharmaceutical Manufacturers Association of Tokyo proposed a specific Light Stability Test that would standardize sample preparation, the light source, the procedure and the interpretation of results for all active ingredients and dosage forms.

3. *Accelerated testing* is designed to estimate, in a short time, the quality of drug in a fixed period of distribution. In this phase, 3 lots of finished product are compared (room time temperature vs. 40 ± 1°C/75 ± 5% RH) for at least 6 months, measuring at least 4 times.

Europe (EEC)

Active ingredients. In the case of a new entity, adequate data must be obtained. For previously marketed substances the scientific literature and/or comparative accelerated studies (a minimum of 2 lots) may be used.

Dosage forms require one study at 25° plus studies under marketing conditions (for at least 6 months) plus optional studies at -20°C, +4°C, 25°C/85% RH, 40°C/85% RH or cycling. Each study must involve 3 lots for new entities and 2 lots for known entities. All studies must be done in the marketed package for characteristics likely to be effected by storage. In addition, the first 2 or 3 production batches must undergo stability testing.

United States

Since 1976, the USP has required all official products to bear an expiration date. In the period between manufacturing and the expiration date, all products listed in the compendia must meet the requirements of the applicable monograph, provided that these products have been stored at the prescribed storage conditions.

The *Code of Federal Regulations* of the United States Government contains guidelines that "establish principles or practices of general applicability and do not include decisions or advice on particular situations." Following the guidelines assures a conduct which is acceptable to the Federal Food and Drug Administration (FDA). Flexibility exists to use alternative procedures not cited in the guidelines. However, it is prudent to discuss such matters with the FDA prior to initiating studies to prevent an expenditure of money and effort for work that the FDA may later determine to be unacceptable [86].

A new feature of the stability guidelines [87] would permit an extension of the expiry date after marketing based on a pre-approved stability protocol and full term shelf-life data (e.g., if original approval was for 2 years dating with 3 years actual room-temperature data the shelf-life could be extended to 3 years).

Emphasis is placed on thorough characterization and stability information on the bulk drug substance. This is equally true with either a brand new chemical entity or a generic drug, domestically or foreign sourced.

The United States Food and Drug Administration recognizes three types of injectable products.

Pre-1938 drugs
New Drug Applications (NDA)
Abbreviated New Drug Applications (ANDA)

New injectable products of drugs first marketed before 1938, marketed in glass containers, are exempted (not covered) by NDA regulations. Pre-1938 injectable drugs marketed in plastic containers are covered under NDA regulations.

An NDA is the normal form under which an injectable drug would be approved in the USA. Abbreviated NDAs are submissions by potential competitors of exact copies of currently marketed products (in formula, package and labelling). They are approved by the Generic Division of FDA and have different stability requirements than NDAs. NDAs are reviewed by an FDA division specializing in disease states (such as cardiovascular or infectious diseases).

Specific comments under parenterals are divided into small volume (SVP) and large volume (LVP) products. By USP definition, SVPs are 100 ml and less and LVPs are greater than 100 ml in volume. Guidelines for stability and assurance of sterility are summarized in Tables 16 and 17 for SVPs.

The following guidelines have been adopted by the Generic Division of FDA for approval of Abbreviated New Drug Applications.

Pre-Marketing

1. Demonstrate adequate stability of the new drug substance using the 8 attributes listed in Table 16.
2. A "conditional" expiration date will be granted based on "challenge" conditions (in lieu of room temperature data). Challenge conditions will be 37 to 40°C (or as appropriate) at 75% RH (as appropriate) at initial, 1, 2, and 3 month intervals. At least one of the three lots must be made in the production facility.

Table 16 FDA Stability Guidelines for Small Volume Parenterals

A.	All products	
	Strength	pH
	Appearance	Sterility
	Color	Pyrogens
	Clarity	Particulate matter
	Store inverted or on side	
B.	Powder and freeze-dried products	
	Residual moisture	
	Reconstituted stability	

Source: Ref. 88.

Table 17 Guidelines for Assurance of Sterility for Small Volume Parenterals

Compendial sterility test (as intervals)
Examination/qualification of container/closure system
Testing for preservative (if present)
or
Assurance of terminal lethality (e.g., F_0, mrads)

Source: Ref. 88.

3. If a product must be reconstituted before use, an additional study must be performed on the reconstituted product.

Post-Marketing

1. The first three marketable production lots of the product should be placed on stability at room temperature. Testing should be done at initial, 3, 6, 9, 12, 18, and 24 months, and yearly thereafter until the expiration date.
2. When more than one package size is marketed, the first 3 production lots of the smallest and largest package size should be placed on stability.
3. If more than one container/closure system is used, stability data must be obtained for each.

B. Storage Temperatures

Product stability studies for a new product containing a new chemical entity fall into three general categories: (1) initial accelerated testing to screen various formulas and obtain a general profile of the stability of the formulated drug; (2) longer term pre-market testing of the formula(s) to establish the specific storage conditions and expiration dating for the drug product; and (3) post-marketing stability on production manufactured batches to assure that there are no differences from the pre-marketed R&D laboratory and pilot batches.

Pharmacopeias vary in their definition of "controlled room temperature." For example, the USP is 15 to 30°C, the European Pharmacopeia is 15 to 25°C. The Japanese Pharmacopeia defines "ordinary temperature" as 15 to 25°C.

The United States Food and Drug Administration has specifically mentioned temperatures in the stability guidelines. However, many firms market parenteral pharmaceutical products in other countries. In fact, worldwide or multiregional marketing is not uncommon. The question then arises, are the FDA guidelines sufficient on a worldwide basis? As articulated by Futscher, et al. [88] and later Grimm [89], there are four climatic zones: Temperate, Mediterranean/Subtropical, Hot/dry and Hot/humid.

Temperature and humidity markedly influence chemical, physical, organoleptic, and microbiological attributes of pharmaceutical dosage forms. Climatic data are available for all countries. Generally, if marketing a product only in the United States 25°C/50% RH are appropriate conditions for storage of samples simulating room temperature. However, if the product will be marketed on a worldwide basis, the proper storage conditions would be 30°C and 75% RH (see table 18).

A practical approach would be to build this variation into one test station (25°C) rather than two (25 and 30°C). The usual approach in stability testing is to carefully control (minimize) temperature fluctuation at each temperature station (25°C, 40°C, 50°C, etc.). If the method of Carstensen and Rhodes [90] for cycling around the controlled room temperature by ±5°C (e.g., 25 ± 5°C) were used, this would be a "reasonable worst case" and would build a conservative bias into products distributed in the United States as well as cover all the extreme cases on a worldwide basis (see Table 19).

C. Solutions

The stability of the majority of injectable products (i.e., solutions) should be evaluated by several parameters. These parameters include potency, pH, color, clarity, odor, stopper appearance, particulate matter, toxicity, container/closure integrity, and preservative effectiveness. As with other dosage forms, a variety of time, temperature, and humidity conditions should be used when predicting the stability of injectable drug products. A brief discussion of the significance of each attribute follows.

Most injectable products are permitted, by either the compendia or government regulations, to contain not less than 90% of the label claim of active ingredient at the expiration date. A stability-indicating assay is critical to determining compliance with this requirement. In recent years, high-performance liquid chromatography (HPLC) methods have been widely used for this purpose. In addition to determining accurately the amount of active ingredient in this product, HPLC assays, when combined with isolation and identification techniques, can be used to identify and quantitate known breakdown products. Knowledge of the breakdown products is very important when evaluating toxicology and chemical degradation data. Actually, the majority of stability fail-

Table 18 Conditions of Storage for Climatic Zones

Climatic zone	Conditions months/temperature	Kinetic average temperature
Temperate	8M-19°C, 3M-23°C, 1M-25°C	20.8°C
Mediterranean/Subtropical	6M-21°C, 4M-26°C, 2M-30°C	25.1°C
Hot/dry	4M-25°C, 4M-30°C, 4M-34°C	30.3°C
Hot/humid	4M-27°C, 4M-29°C, 4M-31°C	29.1°C

Source: Ref. 89.

Table 19 Comparison of Cyclic Versus Constant Temperature Storage (k = 0.01% per day)

Activation energy, E_a. (kCal/mole)	k-Static (%/day)	k-Cyclic (%/day)	Loss after 3 years		% Increase
			Static	Cyclic	
10	0.01	0.01019	10.95	11.16	1.9
15	0.01	0.01041	10.95	11.38	3.9
20	0.01	0.01075	10.95	11.77	7.5
25	0.01	0.01120	10.95	12.27	12.1
30	0.01	0.01177	10.95	12.89	17.7

Source: Ref. 90.

ures or limitations with injectable products is due to factors other than low potency.

A change in the pH of a drug solution during stability testing can be indicative of either degradation of the active ingredient or interaction of one or more of the constituents of the solution with either the container (plastic or glass) or the rubber closure. For example, a significant increase in the pH of a neutral or acidic solution could indicate that alkaline materials are leaching from the glass container into the solution. This would be particularly true if type III glass (soda-lime) is used instead of type I glass (borosilicate). Another example would be lowering of pH of a highly alkaline sodium barbiturate derivative, resulting in precipitation of the free acid of the drug. If a change in pH becomes important to control, a buffer system (previously discussed) may be required.

Color changes frequently occur with solutions of injectable drugs stored at high temperatures (40°C or higher). This is usually due to accelerated decomposition of the drug (especially if it degrades by oxidation) or interaction of metals from the rubber closure with one or more of the ingredients in the solution. A color change can usually be prevented by replacing the air (oxygen) in the vial or ampul headspace with an inert gas, such as nitrogen or carbon dioxide, or by the addition of a chelating agent, such as ethylenediaminetetracetic acid, to the solution.

Turbidity in a solution can be seen utilizing the Tyndall effect. Suspended particles adsorb or scatter (diffract, refract, and reflect) light. Turbidity is the reduction in light transmission through the solution as a result of suspended particles. Generally, solutions of injectable drugs should maintain a light transmission of 70% or more during the shelf life of the product. Most solutions undergo a decrease in transmission with time, as measured in a nephelometer. Ideally, a solution immediately after manufacturing will have light transmission of 92 to 97% and will not decrease to less than 70% over a 3 to 5 year period. Factors that can cause an increase in turbidity include generation of particulate matter (usually from a solution/container interaction),

precipitation of a constituent of the solution because of drug/preservative, drug/closure, preservative/closure or similar reaction, or growth of microorganisms, generally due to preservative loss.

Periodically, a container should be opened and examined for change in odor. Sometimes decomposition can be detected, particularly in solutions with sulfur-containing drugs or antioxidants. Rubber closures should be removed periodically and examined visually and microscopically for changes in color and texture. Many drug solutions, particularly those of high or low pH or oil-based, interact with rubber closures. This interaction can be accelerated by storing vials inverted under various conditions of temperature. Detectable changes in the appearance of stoppers should be investigated to determine if there are changes in properties of the product.

Several batches placed on stability should be characterized for the level of particulate matter 10 μm and larger. Periodically, these batches should be reexamined under "normal" storage conditions (i.e., 5°C and 25°C) utilizing similar methodology, for any change in particulate levels. Particulate methodology is difficult to reproduce, even under carefully controlled conditions, and care must be excercised when evaluating the results obtained. Numbers may increase (most likely) or decrease (least likely) depending on solution/container interaction, ingredient instability brought on by pH or other changes or solubilization of drug with time.

LD_{50} or LD_0 (safety test) data should be gathered initially and at intervals during the storage period to assure that no toxic breakdown or interaction products are forming. If the LD_{50} value changes significantly, the formulator should confer with chemists and toxicologists who are knowledgeable about the drug to explain this change in the safety test data.

Products in multiple-dose vials are preserved primarily to prevent the growth of microorganisms inadvertently introduced during the use of the product in the hospital, clinic, or physician's office. Therefore, a microbial challenge test must be conducted initially and at yearly intervals on samples stored at ambient (25°C) conditions. Procedures to be used are found in USP XXII. Antimicrobial agents can decompose, be rendered ineffective due to pH changes or chelation with metals leached from rubber closures, or be absorbed into rubber closures. Early in the development of a product, the minimum effective concentration (MEC) or minimum inhibition concentration (MIC) of antimicrobial agent needed in the formula must be determined. A stability indicating assay should be developed for the antimicrobial agent and samples stored at normal storage conditions (5°C and 25°C) should be assayed at regular intervals to monitor the level of antimicrobial agent. Normally, this level will gradually decrease during storage. Of course, the level should not be permitted to fall below the MIC during its shelf life.

D. Sterile Solids

Reconstituted sterile injectable solids should be inspected for most of the attributes that pertain to liquids: potency, pH, color, clarity, odor, stopper appearance, particulate matter, and toxicity. In addition, the dry sterile powder must be evaluated for color uniformity, moisture content, and reconstitution rate. Most of these parameters were discussed in the preceding section under solutions but two that deserve additional discussion are moisture content and reconstitution rate.

Most dry solids, whether dry fill, spray dried, or freeze-dried, have an optimal moisture range for stability. With rare exceptions, vials of dry sterile solids utilize butyl rubber closures with low MVT. Not only can the presence of excess moisture accelerate chemical degradation, but often determines the polymorphic or hydrate form of the drug. The crystalline form of the drug is often vital to the chemical stability of the drug, examples being the cephalosporin antibiotics. Injectible drugs that require reconstitution should dissolve rapidly, generally in 1 min or less. Chemical changes, such as formation of less soluble degradation products or a different crystalline form, can cause a slowing of the reconstitution rate.

E. Suspensions

Parenteral suspensions exhibit instability in ways not applicable to solutions and dry solids. Physical properties such as viscosity, rheological behavior, suspendibility, syringability, and particle size distribution need to be monitored as a part of a stability program. Figure 31 shows typical graphs of these properties for prednisolone acetate suspension.

The viscosity of a suspension is a measure of the resistance to flow upon shear. Through the use of a recording viscometer, the rheological behavior

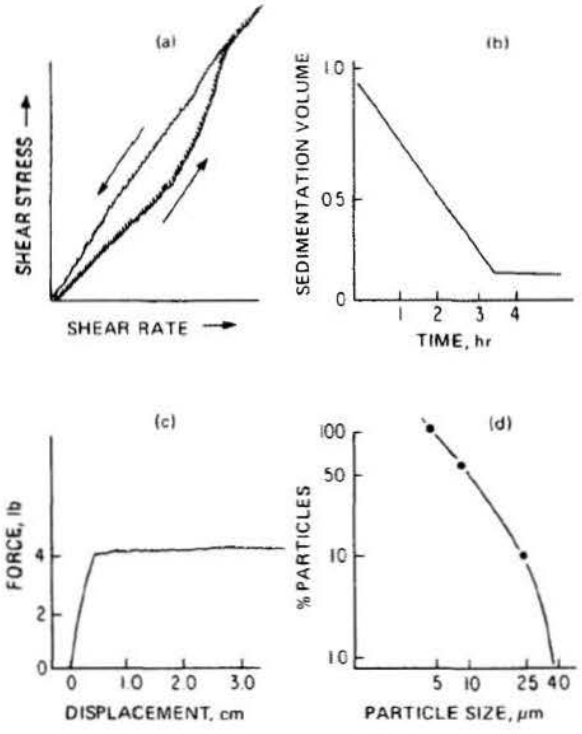

Figure 31 Physical properties of a prednisolone acetate suspension.

as well as viscosity can be determined. As shown in Figure 31a, the flow behavior for prednisolone acetate suspension is nearly Newtonian with a slig hysteresis loop. The linear and consistent sedimentation rate, as shown in Figure 31b, indicates stability of particle size and particle size distribution and, further, that particle aggregation is minimal or nonexistent. Figure 3 shows a force-displacement profile of the ejection of the suspension from a syringe. From this the force required to eject the suspension can be deter mined. A consistent force and shape of the curve is indicative of physical stability. Particle size distribution is shown in Figure 31d.

F. Stability Protocol

A complete stability evaluation on the final formulation in the proposed fina package includes storing representative samples at at least three elevated temperatures and room temperature and in the light. The accelerated sche (i.e., samples at elevated temperatures and in the light) generally lasts fo 12 weeks. A typical schedule is shown in Table 20.

From the data collected over 12 weeks the decision to continue the proc can be made. Most degradation being hydrolytic in nature follow first-orde or pseudo-first-order kinetics. The chemical stability of the drug substan can be predicted by first plotting the temperature data as shown in Figure and determining the rate constants from the slopes of the lines. The exam shown is for a first-order reaction in which the substance degrades to pro ucts at a rate that is directly proportional to the concentration of the react substance.

$$\text{Rate} = \frac{dC}{dt} = kC \qquad (3$$

where

C = concentration of reacting substance
k = reaction rate
t = time

Converting Equation (31) to

$$\frac{dC}{C} = -k\,dt \qquad (3$$

gives

$$\log C = \frac{k}{2.303}\,t + \text{constant} \qquad (3$$

By plotting the concentration versus time on semilog graph paper, the rea tion rate can be determined from the slope of the line.

The influence of temperature on reaction rate has been shown by Arrh ius.

$$\log k = -\frac{\Delta H_a}{2.303R}\,\frac{1}{T} + \log S \qquad (3$$

Table 20 Typical Accelerated Stability Schedule for a Parenteral Solution[a,b]

Time (weeks)	Room temperature	Temperature (°C) 40	50	60	Light
0	X				
1			X	X	X
3	X	X	X	X	
6	X	X	X	X	X
12	X	X			X

[a]X, perform all determinations.
[b]Continue study at room temperature for 6, 12, 18, 24, 30, and 36 months.

where

R = gas constant (1.987 cal deg^{-1} mol^{-1})
T = absolute temperature
S = frequency factor
ΔH_a = heat of activation

By plotting the rate constants obtained at accelerated temperatures versus the reciprocal of absolute temperature (Fig. 33), the heat of activation can be calculated from the slope. The value represents the energy the molecules

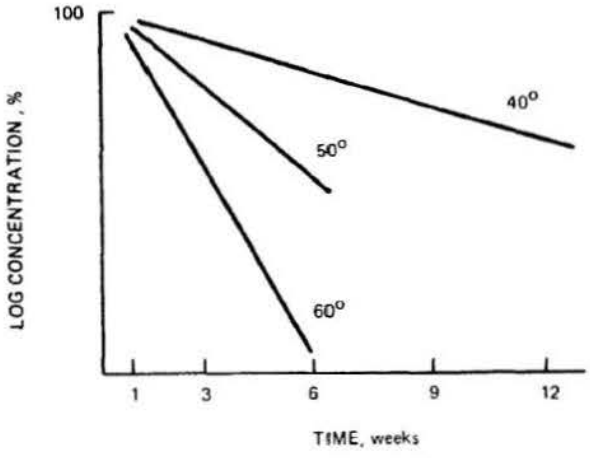

Figure 32 Typical first-order degradation plot of concentration versus time at three temperatures.

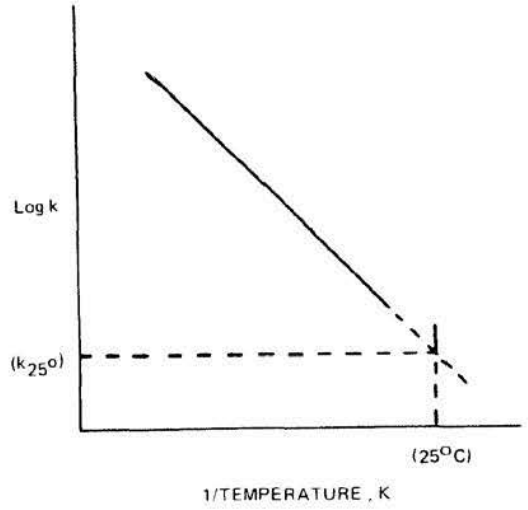

Figure 33 Arrhenius-type plot of log rate constant versus the reciprocal of absolute temperature.

must reach to undergo reaction. By extrapolating the line as shown to room temperature, the rate constant at ambient conditions can be determined. Fro this, the time for 10% degradation can be calculated using the following expre sion:

$$t_{10\%} = \frac{2.303}{k_{25^\circ C}} \log \frac{100}{90} \qquad (35$$

In addition to the drug, the loss of antimicrobial agents and antioxidants tha can be absorbed or consumed should be tested in the same manner. Such accelerated treatment allows decisions to be made on further plans for the product. For example, if the company is confident of the 12 week data, plan to submit as NDA of ANDA can proceed. Most likely by the time the FDA co act on the submission, 6 month or 1 year room-termperature data would be available. Generally, the FDA accepts accelerated data contingent upon re-ceiving sufficient room temperature information. The expiration date will de-termine the amount of information required. With less than 1 year's data, an expiration date or no more than one year will be allowed. As sufficient data are accumulated, a longer expiration date can be included. For more compre hensive treatment on stability evaluation, readers are encouraged to consult other texts [91,92].

V. PROCESS EFFECTS

The processing of parenteral products has been covered elsewhere in this textbook, but some specific cautions associated with the effects on formulatic

will be highlighted. Parenterals are processed by either nonaseptic methods, and terminal sterilization or aseptically using filtration sterilization. Although parenteral solutions filled into ampuls or vials for terminal sterilization do not require aseptic processing, the final product must be sterile and free of pyrogens and particulate matter. Consequently, containers and closures are generally subjected to final rinsing with water for injection. 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 min could give rise to degradation processes and interactions with the container. Additionally, materials could leach form the rubber closure. In addition to loss of drug, antimicrobial agents and antioxidants can be absorbed or consumed during sterilization.

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:

1. Scale-up procedures
2. Preliminary technical documentation
3. Design of processing and validation protocols
4. Qualification/validation runs
5. Final technical documentation and authorizations

The overall approach must be *organized, scientific,* and *thorough.*

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