The Theory and Practice of Industrial Pharmacy

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Solutes

The physical and chemical purity of solutes used for sterile preparations must also be exceptional. Obviously, contaminants entering a product with a solute have the same effect as if they entered via the vehicle. Even small traces of contaminants may be detrimental to products, necessitating purification of the solute. For a few substances (for example, ascorbic acid and calcium gluconate), special parenteral grades are commercially available.

In addition, solutes should be free from microbial and pyrogenic contamination. This entails not only proper quality of the chemical as procured but storage conditions designed to prevent contamination, particularly after a container has been opened. Preferably, production lots should be designed to use the entire contents of packages of chemicals whenever possible.

Added Substances. Substances added to a product to enhance its stability are essential for almost every product.[13] Such substances include solubilizers, antioxidants, chelating agents, buffers, tonicity contributors, antibacterial agents, antifungal agents, hydrolysis inhibitors, antifoaming agents, and numerous other substances for specialized purposes. At the same time, these agents must be prevented from adversely affecting the product. In general, added substances must be nontoxic in the quantity administered to the patient. They should not interfere with the therapeutic efficacy nor with the assay of the active therapeutic compound. They must also be present and active when needed throughout the useful life of the product. Therefore, these agents must be selected with great care, and they must be evaluated as to their effect upon the entire formulation. An extensive review of excipients used in parenteral products and the means for adjusting pH of these products has recently been published and should be referred to for more detailed information.[14] Table 22-1 provides a list, adapted from that review, of excipients commonly used in commercial parenteral products.

Antibacterial Agents. Antibacterial agents in bacteriostatic concentration must be included in the formulation of products packaged in multiple dose vials, and are often included in formulations to be sterilized by marginal processes or made by aseptic manipulation. The requirements of activity, stability, and effectiveness of antibacterial agents in parenterals have been reviewed in published papers.[15–17]

Antioxidants. Antioxidants, included in many formulations to protect a therapeutic agent susceptible to oxidation, particularly under the accelerated conditions of thermal sterilization, may function in at least two ways., i.e., (1) by being preferentially oxidized (reducing agents) and thereby gradually used up, or (2) by blocking an oxidative chain reaction in which they are not usually consumed. In addition, certain compounds have been found to act as synergists, increasing the effectiveness of antioxidants, particularly those blocking oxidative reactions. A fourth group of compounds are useful in this connection in that they complex with catalysts that otherwise would accelerate the

Table 22-1. *Excipients Used for Commercial Parenteral Products*

Excipients	*Concentration Range (%)*
Antimicrobial Preservatives	
Benzyl alcohol	0.5–10.0
Benzethonium chloride	0.01
Butylparaben	0.015
Chlorobutanol	0.25–0.5
Metacresol	0.1–0.25
Methylparaben	0.01–0.18
Myristylgamma picolinium chloride	0.17
Phenol	0.065–0.5
Phenylmercuric nitrate	0.001
Propylparaben	0.005–0.035
Thimerosal	0.001–0.02
Solubilizers, Wetting Agents, or Emulsifiers	
Dimethylacetamide	0.01
Dioctyl sodium sulfosuccinate	0.015
Egg yolk phospholipid	1.2
Ethyl alcohol	0.61–49.0
Ethyl lactate	0.1
Glycerin	14.6–25.0

Excipients	*Concentration Range (%)*
Solubilizers, Wetting Agents, or Emulsifiers—continued	
Lecithin	0.5–2.3
PEG-40 castor oil	7.0–11.5
Polyethylene glycol 300	0.01–50.0
Polysorbate 20	0.01
Polysorbate 40	0.05
Polysorbate 80	0.04–4.0
Povidone	0.2–1.0
Propylene glycol	0.2–50.0
Sodium desoxycholate	0.21
Sorbitan monopalmitate	0.05
Theophylline	5.0
Buffers	
Acetic acid	0.22
Adipic acid	1.0
Benzoic acid and sodium benzoate	5.0
Citric acid	0.5
Lactic acid	0.1
Maleic acid	1.6
Potassium phosphate	0.1
Sodium phosphate monobasic	1.7
Sodium phosphate dibasic	0.71
Sodium acetate	0.8
Sodium bicarbonate	0.005
Sodium carbonate	0.06
Sodium citrate	4.0
Sodium tartrate	1.2
Tartaric acid	0.65
Bulking Substances or Tonicity Modifiers	
Glycerin	1.6–2.25
Lactose	0.14–5.0
Mannitol	0.4–2.5
Dextrose	3.75–5.0
Sodium chloride	varies
Sodium sulfate	1.1
Sorbitol	2.0
Suspending Agents	
Gelatin	2.0
Methylcellulose	0.03–1.05
Pectin	0.2
Polyethylene glycol 4000	2.7–3.0
Sodium carboxymethylcellulose	0.05–0.75
Sorbitol solution	50.0
Chelating Agents	
Edetate disodium	0.00368–0.05
Edetate calcium disodium	0.04
Edetate tetrasodium	0.01
Local Anesthetics	
Procaine HCl	1.0
Benzyl alcohol	5
Stabilizers	
Creatinine	0.5–0.8
Glycine	1.5–2.25
Niacinamide	1.25–2.5
Sodium acetyltryptophanate	0.53
Sodium caprylate	0.4
Sodium saccharin	0.03

Adapted from Wang, Y.J., and Kowal, R.R.: J. Parent. Drug Assoc., 34:452, 1980.

oxidative reaction. Because of the differences in action, combinations of these agents are sometimes used. In Table 22-2, the more commonly employed antioxidants are listed according to the above four groupings. The reader is referred to the literature for more details concerning antioxidants and their activities.[18–20]

It should also be mentioned that for those products in which oxygen enters into a degradative reaction, an antioxidant effect can be achieved by displacing oxygen (air) from contact with the product. Usually, this is accomplished by saturating the liquid with either nitrogen or carbon dioxide and sealing the final container after displacing the air above the product with the gas.

Higuchi and Schroeter have warned of the reactivity of bisulfites with drug molecules,[21] and Halaby and Mattocks have warned of the potential toxicity of sodium bisulfite absorbed from peritoneal dialysis solutions.[22]

Buffers. Buffers are added to maintain a required pH for many products; a change in pH may cause significant alterations in the rate of degradative reactions. Changes in pH may occur during storage as a result of the dissolving of glass constituents in the product, release of constituents from rubber closures or plastic components in contact with the product, dissolving of gases and vapors from the airspace in the container and diffusion through the rubber or plastic component, or reactions within the product. Buffers must have the capacity to maintain the pH of the product against these influences, but not enough to prevent the body fluids from overwhelming the buffer following administration. In most cases, the biologic effectiveness of the drug is maximum at or near the biologic fluid pH rather than at the stabilizing pH of the injected product.

Acetates, citrates, and phosphates are the principal buffer systems used, but buffer systems making use of other ingredients in the formulation are often used to reduce the total number of ingredients in the product. Buffer systems must be selected with consideration of their effective range, concentration, and chemical effect on the total product. These factors have been reviewed by Windheuser.[23]

Tonicity Contributors. Compounds contributing to the isotonicity of a product reduce the pain of injection in areas with nerve endings. Buffers may serve as tonicity contributors as well as stabilizers for the pH. Other added substances also contribute to the colligative properties of the preparation. Whenever possible such dual activity is desirable.

Although the freezing point depression of the solution is most frequently used to determine whether a solution is isotonic, isotonicity actually depends on the permeability of a living semipermeable membrane that separates the solution from a biologic cell system. Most frequently, for sterile pharmaceutical preparations, the membrane concerned is the one enclosing the red blood cells. Therefore, a preparation cannot be considered to be isotonic until it has been tested in a biologic system. A hemolytic method, using red blood cells, has been described.[24,25] Isotonicity values for various drugs have been recorded.[26-29] Testing by such a method becomes even more important when all or part of the water is replaced with another solvent, since dissociation is different when water is displaced by another solvent.

TABLE 22-2. *Antioxidants Used in Sterile Products*

Compound	*Usual Concentration (%)*
Antioxidants (reducing agents)	
Ascorbic acid	0.02–0.1
Sodium bisulfite	0.1–0.15
Sodium metabisulfite	0.1–0.15
Sodium formaldehyde sulfoxylate	0.1–0.15
Thiourea	0.005
Antioxidants (blocking agents)	
Ascorbic acid esters	0.01–0.015
Butyl hydroxytoluene (BHT)	0.005–0.02
Tocopherols	0.05–0.075
Synergists	
Ascorbic acid	0.01–0.05
Citric acid	0.005–0.01
Citraconic acid	0.03–0.45
Phosphoric acid	0.005–0.01
Tartaric acid	0.01–0.02
Chelating agents	
Ethylenediaminetetraacetic acid salts	0.01–0.075

Containers

Containers are in intimate contact with the product. No container presently available is totally nonreactive, particularly with aqueous solutions. Both the chemical and physical characteristics affect the stability of the product, but the physical characteristics are given primary consideration in the selection of a protective container.

Glass containers traditionally have been used for sterile products, many of which are closed with rubber stoppers. Interest in plastic con-

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