

chosen for a particular formula.^{46,47} In addition to presenting a health hazard to the user, microbial growth can cause marked effects on product stability.

Numerous sources of contamination exist. Including among these are raw materials, processing containers and equipment, the manufacturing environment, operators, packaging materials, and the user.

Manufacturing techniques to minimize microbial contamination are presented under the heading "Manufacturing Considerations." The remainder of this section deals with preservative systems for liquid products.

An ideal preservative can be qualitatively defined as one that meets the following three criteria:

1. It must be effective against a broad spectrum of microorganisms.
2. It must be physically, chemically, and microbiologically stable for the lifetime of the product.
3. It must be nontoxic, nonsensitizing, adequately soluble, compatible with other formulation components, and acceptable with respect to taste and odor at the concentrations used.

No single preservative exists that satisfies all of these requirements for all formulations. The selection of a preservative system must be made on an individual basis, using published information and "in house" microbiologic studies for guidance. Frequently, a combination of two or more preservatives are needed to achieve the desired antimicrobial effect.

The antimicrobial agents that have been used as preservatives can be classified into four major groupings: acidic, neutral, mercurial, and quaternary ammonium compounds. Table 15-2 lists some representative members of these groupings and the concentration ranges at which they have been used.

The phenols are probably the oldest and best known pharmaceutical preservatives, but are little used in oral pharmaceuticals, owing to their characteristic odor and instability when exposed to oxygen. The more useful members of the series, for this application, are the parahydroxybenzoic acid esters, and the salts of benzoic and sorbic acid. They are adequately soluble in aqueous systems and have been demonstrated to possess both antifungal and antibacterial properties.

Frequently, a combination of two or more esters of parahydroxybenzoic acid are used to

TABLE 15-2. Some Pharmaceutically Useful Preservatives

Class	Usual Concentration (%)
<i>Acidic</i>	
Phenol	0.2-0.5
Chlorocresol	0.05-0.1
O-phenyl phenol	0.005-0.01
Alkyl esters of parahydroxybenzoic acid	0.001-0.2
Benzoic acid and its salts	0.1-0.3
Boric acid and its salts	0.5-1.0
Sorbic acid and its salts	0.05-0.2
<i>Neutral</i>	
Chlorbutanol	0.5
Benzyl alcohol	1.0
β -phenylethyl alcohol	0.2-1.0
<i>Mercurial</i>	
Thimerosal	0.001-0.1
Phenylmercuric acetate and nitrate	0.002-0.005
Nitromersol	0.001-0.1
<i>Quaternary Ammonium Compounds</i>	
Benzalkonium chloride	0.004-0.02
Cetylpyridinium chloride	0.01-0.02

achieve the desired antimicrobial effect. Methyl and propyl parahydroxybenzoic acid, for example, are often used together in a ratio of 10 to 1, respectively. The use of more than one ester makes possible a higher total preservative concentration, owing to the independent solubilities of each, and according to some researchers, serves to potentiate the antimicrobial effect. The solubilities of a series of parabens have been studied at four temperatures. The solubilities were expressed in terms of ideal, actual, and excess free energies.⁴⁸

The remaining three classes of preservatives have been widely used in ophthalmic, nasal, and parenteral products, but have been little used in oral liquids. The neutral preservatives are all volatile alcohols, and their volatility introduces odor problems as well as concern for preservative loss on aging. The mercurials and quaternary ammonium compounds are excellent preservatives. They are, however, subject to a variety of incompatibilities, with mercurials being readily reduced to free mercury and the quaternary compounds being inactivated by a variety of anionic substances. The incompatibilities common to these and other preservatives are discussed by Lachman.⁴⁹

Syrups containing approximately 85% sugar