Secundum Artem

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Current & Practical Compounding Information for the Pharmacist

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Preservatives, Antioxidants and pH

Goal: To provide information for the stability and proper preservation of compounded formulations.

Objectives: After reading and studying the article, the reader will be able to:

1. Discuss the factors to be considered in the selection of a preservative
2. List mechanisms of action and characteristics of an effective preservative
3. Describe when an antioxidant is required for a compounded formulation
4. Describe the importance of pH in pharmaceutical products and preparations
5. List common antioxidants and chelating agents used in both ophthalmic and nasal preparation

PRESERVATIVES

In addition to the stabilization of pharmaceutical preparations against chemical and physical degradation within a formulation, certain liquid and semisolid preparations must be preserved against microbial contamination. Preservatives are typically added to either minimize microbial growth, as is the case with oral liquids, topicals, and the like, or to prevent microbial growth, as is necessary for sterile preparations such as parenterals, ophthalmics, and oral inhalation solutions.

Sterilization and Preservation

Although some types of pharmaceutical products, for example, ophthalmic and injectable preparations, are sterilized by physical methods during preparation, many of them also require an antimicrobial preservative to maintain their aseptic condition throughout storage and use. Other types of preparations that are not sterilized during their preparation but are particularly susceptible to microbial growth because of the nature of their ingredients are protected by the addition of an antimicrobial preservative. Preparations that provide excellent growth media for microbes are most aqueous preparations, especially syrups, emulsions, suspensions, and some semisolid preparations, particularly creams. Certain hydroalcoholic and most alcoholic preparations may not require the addition of a chemical preservative when the alcoholic content is sufficient to prevent microbial growth. Generally, 15% v/v alcohol will prevent microbial growth in acid media and 18% v/v in alkaline media. Most alcohol-containing pharmaceuticals, such as elixirs, spirits, and tinctures, are self-sterilizing and do not require additional preservation. The same applies to other individual pharmaceuticals that by virtue of their vehicle or other formulative agents may not permit the growth of microorganisms.

General Preservative Considerations

Microorganisms include molds, yeasts, and bacteria, with bacteria generally favoring a slightly alkaline medium and the others an acidic medium. Although few microorganisms can grow below pH 3 or above pH 9, most aqueous pharmaceutical preparations are within the favorable pH range and therefore must be protected against microbial growth. To be effective, a preservative agent must be dissolved in sufficient concentration in the aqueous phase of a preparation. Furthermore, only the undissociated fraction or molecular form of a preservative possesses preservative capability, because the ionized portion is incapable of penetrating the microorganism. Thus, the preservative selected must be largely undissociated at the pH of the formulation being prepared. Acidic preservatives like benzoic, boric, and sorbic acids are more undissociated and thus more effective as the medium is made more acid. Conversely, alkaline preservatives are

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less effective in acid or neutral media and more effective in alkaline media. Thus, it is meaningless to suggest preservative effectiveness at specific concentrations unless the pH of the system is mentioned and the undissociated concentration of the agent is calculated or otherwise determined. Also, if formulative materials interfere with the solubility or availability of the preservative agent, its chemical concentration may be misleading, because it may not be a true measure of the effective concentration. It is essential for the compounding pharmacist to examine all formulative ingredients as one affects the other to ensure that each agent is free to do its job. In addition, the preservative must not interact with a container or closure.

In the pharmaceutical development process, the lowest effective concentration of an antimicrobial preservative that is demonstrated to be effective by an antimicrobial preservative effectiveness test should be used. The concentration used should be validated in terms of efficacy and safety, with the effectiveness confirmed to last throughout the intended shelf life of the preparation.

Mode of Action

Preservatives interfere with microbial growth, multiplication, and metabolism through one or more of the following mechanisms:

- Modification of cell membrane permeability and leakage of cell constituents (partial lysis)
- Lysis and cytoplasmic leakage
- Irreversible coagulation of cytoplasmic constituents (e.g., protein precipitation)
- Inhibition of cellular metabolism, such as by interfering with enzyme systems or inhibition of cell wall synthesis
- Oxidation of cellular constituents
- Hydrolysis

Examples of the preservatives and their concentrations commonly employed in pharmaceutical preparations are listed in Table 1. For each type of preparation to be preserved, the compounding pharmacist must consider the influence of the preservative on the comfort of the patient. For instance, a preservative in an ophthalmic preparation must have an extremely low degree of irritant qualities, which is characteristic of chlorobutanol, benzalkonium chloride, and phenylmercuric nitrate, frequently used in ophthalmic preparations. In all instances, the preserved preparation must be biologically tested to determine its safety and efficacy and shelf-tested to determine its stability for the intended shelf life of the preparation.

Preservative Selection

Preservation involves the addition of a substance to a preparation; the choice of preservative to be added depends on the characteristics of the preparation and its acceptability to the patient.

Selection Factors

Factors that must be considered in selecting a preservative include concentration, pH, taste, odor, and solubility. Some preparations, such as syrups are inherently preserved by their high concentration of sugar, which acts as an osmotic preservative. For most preparations, however, a suitable preservative is necessary. In choosing a preservative, the pharmacist must ensure that the compounded preparation is stable. A preservative must be nontoxic, stable, compatible, inexpensive and have an acceptable taste, odor, and color. It should also be effective against a wide variety of bacteria, fungi, and yeasts.

When experience or shelf storage experiments indicate that a preservative is required in a pharmaceutical preparation, its selection is based on many considerations, including some of the following:

- The preservative prevents the growth of the type of microorganisms considered the most likely contaminants of the preparation.
- The preservative is sufficiently soluble in water to achieve adequate concentrations in the aqueous phase of a system with two or more phases.
- The proportion of preservative remaining undissociated at the pH of the preparation makes it capable of penetrating the microorganism and destroying its integrity.
- The required concentration of the preservative does not affect the safety or comfort of the patient when the pharmaceutical preparation is administered by the usual or intended route; that is, it is nonirritating, nonsensitizing, and nontoxic.
- The preservative has adequate stability and will not be reduced in concentration by chemical decomposition or volatilization during the desired shelf life of the preparation.
- The preservative is completely compatible with all other formulative ingredients and does not interfere with them, nor do they interfere with the effectiveness of the preservative agent.
- The preservative does not adversely affect the preparation's container or closure.

Table 1: Preservatives Used in Selected Pharmaceutical Preparations

Preservative	Concentration (%)				
	Liquids	Emulsions	Ointments/ Creams	Parenterals	Ophthalmic/ Nasal/Otic
Alcohol/ethanol	15–20	15–20			
Benzalkonium chloride	0.004–0.02	0.002–0.1	0.01	0.013	0.004 – 0.02
Benzethonium chloride	0.004–0.02	0.005–0.02	0.01	0.01	0.004 – 0.01
Benzoic acid and salts[a]	0.1–0.3	0.1–0.3			
Sodium benzoate	0.1–0.3	0.1–0.3			
Benzyl alcohol	1.0–3.0	1.0–4.0	1	1-2	
Boric acid and salts	0.5–1				
Cetylpyridinium chloride	0.01–0.02	0.01–0.02			
Cetyltrimethyl ammonium bromide	—	0.01–0.02			
Chlorobutanol[b]	0.3–0.5	0.5		0.25–0.5	0.5
Chlorocresol	0.05–0.1			0.1–0.3	
Cresol	0.3–0.5	0.3–0.5	0.3–0.5	0.3-0.5	
Imidazolidinyl urea	—	0.05–0.5			
Metacresol			0.1–0.3	0.1-0.3	
Myristylgamma picolinium chloride	0.17				
Nitromersol	0.001–0.1				
Parabens[c]	0.001–0.2	0.05-0.3	0.001–0.2	0.02–0.2	0.1
Benzyl				0.015	
Butyl		0.02-0.2		0.015	
Methyl		0.05-0.3		0.1–0.2	
Propyl		0.02-0.2		0.02–0.2	
Phenol[d]	0.2–0.5	0.2–0.5	0.2–0.5	0.25-0.5	
o-Phenyl phenol	0.005–0.01				
β-phenylethyl alcohol	0.2–1				
Phenylmercuric acetate/nitrate	0.002–0.005	0.002–0.005	0.002	0.002-0.004	0.004
Sorbic acid and salts	0.05–0.2	0.05–0.2			
Thimerosal	0.001–0.1	0.005–0.02	0.01	0.01	0.01

[a] Benzoic acid/sodium benzoate are most effective at a pH of 4 or below.

[b] The anhydrous form of chlorobutanol should be used if a clear solution is desired in liquid petrolatum. Chlorobutanol needs a pH <5; also, it will sorb to plastic.

[c] Parabens are usually used in pairs. They have low water solubility and poor taste. May degrade at a pH >8; they are best used at a pH range of 4–8. The parabens may interact with certain macromolecular compounds and bind, resulting in a loss of some effectiveness.

[d] Phenol forms an eutectic mixture with a number of compounds and may soften cocoa butter in suppository mixtures. Phenol may precipitate albumin, gelatin, and collodion. A green color may be produced in the presence of alum or borax.

Table 2: Binding Percentages of Parabens with Macromolecular Compounds

Compound	% of Methylparaben Bound	% of Propylparaben Bound
Gelatin	8	11
Methylcellulose	9	13
Polyethylene glycol 4000	16	19
Polyvinylpyrrolidone	22	36
Polyoxyethylene monostearate	45	84
Polyoxyethylene sorbitan monolaurate	57	86
Polyoxyethylene sorbitan monooleate	57	90

Physicochemical Considerations for Common Preservatives

Preservatives have unique characteristics that must be taken into account during the selection process. For example, the anhydrous form of chlorobutanol should be used if a clear solution is desired in liquid petrolatum. Ethylenediamine may irritate the skin and mucous membranes and thus should be used with caution; sodium benzoate is most effective at a pH of 4 or below, and a green color may be produced in the presence of alum or borax. The parabens may interact with certain macromolecular compounds, binding and thereby losing some of their effectiveness (Table 2). Phenol forms a eutectic mixture with a number of compounds and may soften cocoa butter in suppository mixtures. Also, phenol may precipitate albumin, gelatin, and collodion.

Quaternary Ammonium Compounds

Benzalkonium chloride is an antimicrobial agent commonly used as a preservative. It acts by emulsification of the bacterial cell walls, probably the cell membrane lipids. Ethylenediaminetetraacetic acid (EDTA) is often added in concentrations ranging from 0.01% to 0.1% to enhance the activity of benzalkonium chloride against *Pseudomonas aeruginosa*. Listed incompatibilities include aluminum, anionic materials, citrates, cotton, fluorescein, hydrogen peroxide, hydroxypropyl methylcellulose, iodides, kaolin, lanolin, nitrates, high concentrations of nonionic surfactants, permanganates, protein, salicylates, silver salts, soaps, sulfonamides, tartrates, zinc oxide, and zinc sulfate.

Benzethonium chloride is a detergent antiseptic with the same limitations and behavior characteristics as benzalkonium chloride. It is incompatible with soaps. One advantage of benzethonium chloride is that its germicidal activity increases with an increase in pH. For example, at pH 10 it is several times more active against selected bacteria than at pH 4.

Chlorobutanol

Chlorobutanol is both antibacterial and antifungal. Its antibacterial effectiveness is reduced above pH 5.5. Aqueous solutions of chlorobutanol will degrade in the presence of hydroxide ions. Chlorobutanol aqueous solutions have good stability at pH 3, but stability decreases with an increase in pH. Chlorobutanol may diffuse through polyethylene or other porous containers, resulting in a decreased concentration and effectiveness. Incompatibilities include plastic vials, rubber stoppers, bentonite, magnesium trisilicate, polyethylene, and polyhydroxyethylmethacrylate (in some soft contact lenses). Some antimicrobial activity is lost on contact with carboxymethylcellulose or polysorbate 80 because of sorption or complex formation. Greater antimicrobial effectiveness can be obtained by combining 0.5% chlorobutanol with 0.5% phenylethanol. The anhydrous form of chlorobutanol should be used if a clear solution is desired in a liquid petrolatum vehicle.

Parabens

Methylparaben is most effective in solution between pH 4 and 8; its efficacy decreases at higher pH levels. In aqueous solution it can be autoclaved and it is stable in aqueous solution in the pH range of 3 to 6 for up to 4 years at room temperature. Methylparaben is incompatible with nonionic surfactants (its antimicrobial activity is reduced), bentonite, magnesium trisilicate, talc, tragacanth, sodium alginate, essential oils, sorbitol, and atropine. It may sorb to some plastics and is discolored in the presence of iron.

Propylparaben is also most effective in solution between pH 4 and 8; its efficacy decreases at higher pH levels. It can be autoclaved in aqueous solutions of pH 3 to 6 without decomposition; aqueous solutions within this pH range are stable for up to 4 years. Propylparaben is incompatible with nonionic surfactants (reduced effectiveness); in addition, sorption has been reported to magnesium aluminum silicate, magnesium trisilicate, yellow iron oxide, and ultramarine blue. Discoloration in the presence of iron and hydrolysis by weak alkalis and strong acids can also occur. Some plastics will adsorb propylparaben. Sodium propylparaben is a more water-soluble form that may be used in place of propylparaben, but the pH of the formulation may be increased.

Phenylmercuric Acetate/Nitrate

Phenylmercuric acetate should be protected from light. It is reported to be incompatible with anionic emulsifying agents and suspending agents, tragacanth, starch, talc, sodium metabisulfite, sodium thiosulfate, disodium edetate, the silicates, halides, and some types of filter membranes used for sterilization. Phenylmercuric nitrate is effective over a broad pH range against both bacteria and fungi and is the preferred form in acidic solutions.

The phenylmercuric salts are used in preference to benzalkonium chloride in solutions of salicylates and nitrates, as well as in solutions of physostigmine and epinephrine that contain sodium sulfite. Its solutions can be autoclaved, but significant amounts of the salt may be lost; therefore, they are best sterilized by filtration. Incompatibilities include anionic emulsifying agents and suspending agents, tragacanth, starch, talc, sodium metabisulfite, sodium thiosulfate, disodium edetate, the silicates, halides, and some types of filter membranes used for sterilization.

Thimerosal

Thimerosal is an antibacterial agent with weak bacteriostatic and mild fungistatic properties. It is affected by light.

Preservative Effectiveness Testing (USP General Chapter <51>)

United States Pharmacopeia (USP) tests for the effectiveness of antimicrobial preservatives may be conducted on any formulation that is expected to be prepared in quantity and used for an extended period of time. The purpose of the tests, which can be conducted by a testing laboratory, is to demonstrate preservative effectiveness against five different organisms *(Candida albicans, Aspergillus niger, Escherichia coli, Pseudomonas aeruginosa,* and *Staphylococcus aureus)*. Test results are applicable only to the specific preparation, packaged in the original, unopened containers.

ANTIOXIDANTS

Oxidation and Antioxidants

Antioxidants are added to minimize or retard oxidative processes that occur with some drugs or excipients on exposure to oxygen (air) or in the presence of free radicals. These processes can often be catalyzed by light, temperature, hydrogen ion concentration, presence of trace metals, or peroxides. Oxidation of a preparation may be manifested as an unpleasant odor or taste, discoloration or other change in appearance, precipitation, or even a slight loss of activity.

It is important to remove oxygen from the ingredients before formulation and to minimize the entrapment of air during formulation. To minimize air entrapment, care should be taken to not foam, whip, mix too vigorously, or form a vortex during mixing. Mixing ingredients at lower-than-normal speed in sealed containers works well. For emulsions, a hand homogenizer (producing strong shear forces in a closed space) works well if the product is collected carefully and protected from air. Degradation can be also minimized by filling the container as full as possible, thereby decreasing the headspace, or by replacing the headspace with nitrogen.

The most common approach to minimizing oxidation is to add an antioxidant to the system (Table 3). The selection of an appropriate antioxidant is dependent on several factors, including solubility, location of the agent in the formulation (emulsions), chemical and physical stability over a wide pH range, compatibility, odor, discoloration, toxicity, irritation, potency, effectiveness in low concentrations, and freedom from toxicity, carcinogenicity, and sensitizing effects.

The actual selection of an antioxidant depends on the (1) type of product, (2) route, dose, and frequency of administration, (3) physical and chemical properties of the preservative used, (4) presence of other components, and (5) properties of the closure and container. The effectiveness of antioxidants may actually be decreased in complex systems such as suspensions and emulsions. This decrease may be due to sorption of the antioxidant onto suspended particles or to partitioning of the antioxidant between the phases of an emulsion. Also, it should be noted that antioxidants may sorb to containers and closures.

In general, antioxidants are used in relatively low concentrations, usually from 0.001% to 0.2%. The lowest effective concentration should be used. When formulating a preparation, pharmacists should remember to incorporate the antioxidant early in the compounding process to minimize the extent of oxidation, rather than at the end of preparation when some of the antioxidant will be needlessly used up in counteracting the oxidation that has already occurred. Also, it is usually advisable to use a chelating agent (See Table 4) along with an antioxidant to chelate trace metals that may catalyze an oxidative process.

The formulation of an antioxidant system is accomplished primarily through trial and error. With some experimentation and patience, a suitable, stable system with the required antioxidant properties can be developed.

pH EFFECT

The pH is one of the most important factors affecting the stability of a preparation. The pharmacist can use published pH/stability profiles to determine the pH that will ensure maximum stability. After determining the pH range, the pharmacist can prepare buffers to maintain the pH for the expected shelf life.

The pH is important in drug formulations, especially because it affects drug solubility, activity, absorption, stability, sorption, and patient comfort. pH is related to certain physical characteristics, such as the viscosity of some polymers used as gel-forming agents and in suspensions.

So that a desired solution pH for both solubility and stability can be maintained, many preparations contain buffer systems. The buffer capacity (i.e., the resistance to change on the addition of either an acid or a base) is generally low so that these systems will not alter the pH of the body fluids on injection. Buffer systems are sufficiently strong, however, to resist changes in pH under normal storage and use.

Table 3: Suggested Antioxidants for Use in Pharmacy Compounding

Antioxidant	Mechanism	Solubility			Usual Concentration
		Water	Alcohol	Oil	Range/Comments
Acetone sodium bisulfite	Reducing	Yes	No	No	0.2%–0.4%
Acetylcysteine	True	Yes	Yes	No	0.1%–0.5%
α-Lipoic acid (sodium salt)	—	Yes	—	Yes	—
α-Tocopherol (synthetic)	True	No	Yes	Yes	
α-Tocopherol acetate	True	No	Yes	Yes	≤0.001%
D-α-Tocopherol (natural)	True	No	Yes	Yes	0.05%–0.075%
DL-α-Tocopherol (synthetic)	True	No	Yes	Yes	0.01%–0.5%
Ascorbic acid	Reducing/Synergy	Yes	Yes	No	Soluble in glycerin/propylene glycol
Ascorbyl palmitate	True	Yes	Yes	Yes	
Butylated hydroxyanisole	True	No	Yes	Yes	0.005%–0.02%/Soluble in propylene glycol
Butylated hydroxytoluene	True	No	Yes	Yes	0.005%–0.02%/Soluble in mineral oil
Calcium ascorbate	Reducing	Yes	Yes	—	
Calcium bisulfite	Reducing	Yes	—	—	
Calcium sulfite	Reducing	Yes	Yes	—	
Cysteine	True	Yes	Yes	No	0.1%–0.5%
Cysteine HCl	True/Synergy	Yes	Yes	No	0.1%–0.5%/Bad odor
Dilauryl thiodipropionate	True	No	Yes	Yes	
Dithiothreitol	True	Yes	Yes	No	0.01%–0.1%
Dodecyl gallate	True	No	Yes	Yes	
Ethoxyquin	True	—	—	Yes	
Ethyl gallate	True	SlS	Yes	No	
Gallic acid	—	Yes	Yes	Yes	
Glutathione	True	Yes	—	—	
Gossypol	True	No	Yes	Yes	
Hydroquinone	Reducing	Yes	Yes	Yes	
4-Hydroxymethyl-2,6-di-*tert*-butylphenol	—	Yes	Yes	Yes	
Hypophosphorus acid	—	Yes	—	—	
Isoascorbic acid	Reducing	Yes	—	—	
Lecithin	True	Yes	Yes	Yes	
Monothioglycerol	Reducing	Yes	Yes	—	0.1%–1.0%/Slight odor
β-Naphthol	True	Yes	Yes	Yes	
Nordihydroguaiaretic acid	True	No	Yes	Yes	0.001%–0.01%
Octyl gallate	True	No	Yes	Yes	
Potassium metabisulfite	Reducing	Yes	No	No	
Propyl gallate	True	SlS	Yes	SlS	0.001%–0.15% (≤2.5 mg/kg body weight)
Sesamol	—	—	—	—	
Sodium ascorbate	Reducing	Yes	Yes	No	
Sodium bisulfite	Reducing	Yes	SlS	No	0.05%–1.0%
Sodium formaldehyde sulfoxylate	Reducing	Yes	SlS	—	0.005%–0.15%
Sodium metabisulfite	Reducing	Yes	SlS	—	0.01%–1.0%/Soluble in glycerin
Sodium sulfite	Reducing	Yes	No	No	0.01%–0.2%
Sodium thiosulfate	Reducing	Yes	No	—	
Sulfur dioxide	Reducing	Yes	Yes	Yes	
Tannic acid	Reducing	Yes	—	—	
Thioglycerol	Reducing	Yes	Yes	—	
tert-Butyl-hydroquinone	True	—	—	—	
Thioglycolic acid	Reducing	Yes	Yes	Yes	
Thiolactic acid	Reducing	Yes	Yes	Yes	
Thiosorbitol	Reducing	Yes	Yes	Yes	
Thiourea	Reducing	Yes	Yes	No	0.005%
Tocopherols	True	—	—	Yes	0.05%–0.5%

Table 4: Common Chelating Agents and Synergists Used in Pharmacy Compounding

Chelating Agent	Solubility			Usual Concentration Range/Comments
	Water	Alcohol	Oil	
Alkyl gallates	Yes	Yes	Yes	
Ascorbic acid	Yes	Yes	No	0.02%-0.1%
Boric acid	Yes	Yes	No	
Citric acid	Yes	Yes	-	0.005%-0.01%
Citraconic acid	Yes	Yes	No	0.03%-0.45%
Cysteine	Yes	Yes	No	
EDTA and salts	Yes	Yes	No	0.02%-0.1%
Gluconic acid	Yes	Yes	No	
Glycine	Yes	Yes	-	
Hydroxyquinoline sulfate	Yes	Yes	-	0.005%-0.01%
Maleic acid	Yes	Yes	No	
Phosphoric acid	Yes	Yes	-	0.005%-0.01%
Polysorbates	Yes	Yes	No	
Saccharic acid	Yes	Yes	No	
Tartaric acid	Yes	Yes	-	0.01%-0.02%
Tryptophan	-	Yes	No	

Adjustment of pH is critical for maintaining drugs in solution. A slight increase or decrease in pH can cause some drugs to precipitate from a solution. Conversely, a slight adjustment of pH can aid in solubilizing some drugs. Drug activity can be related to pH, depending on whether the ionized or the nonionized form is desired. Drug stability, in many cases, directly depends on the pH of the environment (dosage form). pH:degradation profiles are of great value in selecting the proper pH for optimum stability of a preparation. Sorption of a drug to various excipients, packaging components, and administration devices can occur. The sorption can be pH related, depending on which species, ionized or nonionized, is sorbed to the material. Patient comfort and, ultimately, compliance can depend on the proper pH of the preparation. In some cases, a compromise must be reached between the drug requirements and patient preferences. Often, pH can be adjusted for optimum drug stability and a low buffer capacity can be used, so that, upon administration, the patient's physiologic buffers will quickly move the pH to the physiologic range.

DOSAGE FORM CONSIDERATIONS

Emulsions

Preservatives may partition into the oil phase of an emulsion and lose their effectiveness. The preservative should be concentrated in the aqueous phase, since this is where bacterial growth usually occurs. In addition, since the un-ionized form of the preservative is more effective against bacteria, most of the preservative should be present in the nonionized state. In order to be effective, the preservative must be neither bound nor adsorbed to any agent in the emulsion or the container. Generally, only preservative in the aqueous phase in the free, unbound, unadsorbed, un-ionized state will be effective in emulsions. The parabens (methylparaben, propylparaben, butylparaben) are among the most satisfactory preservatives for emulsions. Antioxidants used in emulsions include ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, gallic acid 4-Hydroxymethyl-2, 6-di-tert-butylphenol, propyl gallate, sulfites and L-Tocopherol.

Oils and fats can become rancid, which causes the preparation to have an unpleasant odor, appearance, and taste; antioxidants can prevent rancidity.

Ophthalmics

Because most ophthalmic solutions and suspensions are prepared in multiuse containers, they must be preserved. The preservative must be compatible with the active drug as well as with all the other excipients in the preparation. Antioxidants may also be required for some active drug ingredients. Common antioxidants and chelating agents used in ophthalmic and nasal preparations include ethylenediamine tetraacetic acid (0.1%), sodium bisulfite (0.1%), sodium metabisulfite (0.1%), and thiourea (0.1%).

Oral Inhalations

Any oral inhalation preparation that is not in unit dose containers should contain a preservative, especially since they are required to be sterile. The minimum amount of preservative that is effective should be used. If too high a concentration is used, it may initiate a cough reflex in the patient. Also, too high a concentration of certain preservatives that are also surfactants may cause foaming that can interfere with the delivery of the complete dose.

Ointments

Antioxidants, such as butylated hydroxy toluene, are sometimes required to delay the rate of rancidification of selected bases.

Gels

When added to an aqueous system, 0.1% methylparaben or propylparaben is generally an acceptable preservative and does not affect the efficiency of the polymer to maintain viscosity.

Parenterals

In compounding parenteral admixtures, pharmacists must be cognizant of adjuvants such as vehicles, cosolvents, buffers, preservatives, antioxidants, inert gases, surfactants, complexation agents, and chelating agents. The addition of a preserved solution of active drug to sterile water for injection, dextrose 5% in water or 0.9% sodium chloride injection may decrease the concentration of the preservative so it is no longer effective.

Preparations that are packaged in multiple-dose vials are required to contain a preservative to prevent the growth of microorganisms that may be introduced when the container is manipulated. However, the preservatives may not always be compatible with other drugs to which the drug may be added. For example, benzyl alcohol is incompatible with chloramphenicol sodium succinate, and the parabens and phenol preservatives are incompatible with nitrofurantoin, amphotericin B, and erythromycin. When bacteriostatic water for injection is used for reconstitution, it is important to select a product with a preservative that will be compatible with the solution. Preservatives must also be compatible with the container to which the preparation is added and with its closure.

SUMMARY

Preservatives, antioxidants and pH are all factors that are critically important in compounding stable preparations and efficacious preparations. Each formulation must be evaluated based on its composition and characteristics.