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Secundum Artem

Current & Practical Compounding Information for the Pharmacist.

COMPOUNDING OPHTHALMIC LIQUIDS

INTRODUCTION

Ophthalmic solutions are sterile, free from foreign particles and especially prepared for instillation into the eye. Ophthalmic suspensions are sterile liquid preparations that contain solid particles in a suitable vehicle intended for instillation into the eye.

COMPOSITION(S)

In addition to the active drugs, ophthalmic preparations contain a number of excipients, including vehicles, buffers, preservatives, tonicity adjusting agents, antioxidants and viscosity enhancers. Important in the formulation process is the use of ingredients that are nonirritating and compatible with the eyes.

PREPARATION METHODS/TECHNIQUES

All work must be done in a clean-air environment, such as a laminar flow hood, by qualified aseptic compounding pharmacists. The source of all the ingredients must be the highest grade that can be reasonably obtained.

Solutions:

1. Accurately weigh/measure each of the ingredients.
2. Dissolve the ingredients in about 3/4 of the quantity of Sterile Water for Injection and mix well.
3. Add sufficient Sterile Water for Injection to volume and mix well.
4. Determine the pH, clarity and other quality control factors from a sample of the solution.
5. Filter through a sterile 0.2 micron filter into a sterile ophthalmic container.
6. Package and label.
7. If a large number are to be prepared, select a random sample to be checked for sterility and to be assayed.

Suspensions:

1. Accurately weigh/measure each of the ingredients.
2. Mix the ingredients in about 3/4 of the quantity of Sterile Water for Injection and mix well.
3. Add sufficient Sterile Water for Injection to volume and mix well.
4. Determine the pH, and other quality control factors from a sample of the suspension.
5. Package in a suitable container for autoclaving.
6. Autoclave, cool and label.
7. If a large number are to be prepared, select a random sample to be checked for sterility and to be assayed.

Or

1. Accurately weigh/measure each of the ingredients.
2. Sterilize each of the ingredients by a suitable method.
3. Mix the ingredients in about 3/4 of the quantity of Sterile Water for Injection and mix well.
4. Add sufficient Sterile Water for Injection to volume and mix well.
5. Determine the pH, and other quality control factors from a sample of the suspension
6. Package and label.
7. If a large number are to be prepared, select a random sample to be checked for sterility and to be assayed.

PHYSICOCHEMICAL UNIQUENESS OF COMMON INGREDIENTS

Considerations in preparing ophthalmic solutions involve clarity, tonicity, pH/buffers, sterility, preservatives, antioxidants, viscosity enhancers, and proper packaging.

Clarity-Ophthalmic solutions must be free from foreign particles, which is generally accomplished by filtration. The filtration process also helps to achieve clarity of the solution. Table 1 contains a list of usable clarifying agents.

Tonicity-Lacrimal fluid has an isotonicity value equivalent to that of a 0.9% sodium chloride solution. However, the eye can tolerate a value as low as 0.6% and as high as 1.8% sodium chloride equivalency. Some ophthalmic solutions will be hypertonic by nature of the high concentration required of the drug substance. Others will be hypotonic and will require the addition of a sub-

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Beyond-use recommendations can be extended if there is supporting scientific stability information as described in the USP23/NF18.

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stance to attain the proper tonicity range. Sodium chloride, boric acid and dextrose are commonly used. Three hundred mOsm/L is ideal with 200-600 mOsm/L acceptable.

pH and Buffering-Ophthalmic solutions are ordinarily buffered at the pH of maximum stability for the drug(s) they contain. The buffers are included to minimize any change in pH during the storage life of the drug; this can result from absorbed CO_2 from the air or from hydroxyl ions from a glass container. Changes in pH can affect the solubility and the stability of drugs, consequently, it is important to minimize fluctuations in pH. The buffer system should be designed sufficient to maintain the pH throughout the expected shelf-life of the product but with a low buffer capacity so as soon as the ophthalmic solution is dropped into the eye, the buffer system of the tears will rapidly bring the pH of the solution back to that of the tears. This is accomplished by using as low a concentration of the buffers salts as possible but still be effective. Generally a buffer capacity less than 0.05 is desired. pH generally in the range of 4-8 is considered optimum.

Sterility-Ophthalmic solutions must be sterile. Sterility is best achieved through sterile filtration using a sterile membrane filter of 0.45 or 0.2 micron pore size and filtering into a sterile container. Other methods of sterilizing ingredients or components of ophthalmics that can be used by compounding pharmacists include dry heat, steam under pressure (autoclaving) and gas sterilization (ethylene oxide).

Preservation-Since most ophthalmic solutions/suspensions are prepared in multiple use containers, they must be preserved. The selected preservative must be compatible with the active drug as well as all the other excipients in the product. Common preservatives for ophthalmic products are shown in Table 2.

Antioxidants may be required for selected active drug ingredients. Tables 3 contains antioxidants that can be used in ophthalmic preparations.

Viscosity enhancers-An increase in the viscosity of ophthalmic products will result in a longer residence time in the eye, providing a longer time for drug absorption and effect. Numerous materials are used, among which methylcellulose is the most common, generally in a concentration of about 0.25% if the 4000 cps grade is used. If methylcellulose is autoclaved, it will come out of solution. However, it can be redispersed after cooling, especially if placed in a refrigerator. Hydroxypropyl methylcellulose in the range of 0.5 to 1% is a good viscosity enhancer, while polyvinyl alcohol 0.5 to 1.5% w/v is an alternative. Solution viscosity in the range of 25-50 cps is common. It is important that solution clarity be maintained with the use of these viscosity enhancers. Suitable viscosity increasing additives are shown in Table 4.

Packaging of ophthalmic solutions is appropriately done in sterile dropper bottles or individual doses can be placed in sterile syringes, without needles.

Ophthalmic suspension particles must be of such a size that they do not irritate and/or scratch the cornea, therefore a micronized form of the drug is required. Ophthalmic suspensions must also be free from agglomeration or caking.

INCOMPATIBILITIES

Zinc salts can form insoluble hydroxides at a pH above 6.4, so a Boric Acid Solution vehicle may be selected. It also has a lower pH (about pH 5) and slight buffering action.

Nitrates or salicylates are incompatible with solutions of benzalkonium chloride, therefore it should be replaced with 0.002% phenylmercuric nitrate.

Sodium chloride cannot be used to adjust the tonicity of silver nitrate solutions since silver chloride would precipitate. Sodium nitrate should be used to adjust the tonicity and phenylmercuric nitrate can be used as the preservative in this situation.

STORAGE/LABELING

Generally, ophthalmic preparations should be stored at either room or refrigerated temperatures and should not be frozen.

STABILITY

Beyond-use dates for water-containing formulations is not later than 14 days, when stored at refrigerated temperatures, for products prepared from ingredients in solid form. If nonaqueous liquids, the beyond-use recommendation is not later than 25% of the time remaining until the products expiration date or 6 months, whichever is earlier. For all others, the recommended beyond-use recommendation is the intended duration of therapy or 30 days, whichever is earlier. These beyond-use recomendations can be extended if there is supporting valid scientific stability information, as explained in the General Compounding Chapter of the United States Pharmacopeia 23/National Formulary 18.

EXAMPLE VEHICLES

Isotonic Sodium Chloride Solution		
Sodium Chloride USP		0.9 g
Benzalkonium Chloride		1:10,000
Sterile Water for Injection	qs	100 mL
Boric Acid Solution		
Boric Acid USP		1.9 g
Benzalkonium Chloride		1:10,000
Sterile Water for Injection	qs	100 mL
Rx Artificial Tears		
Polyvinyl alcohol		1.5%
Povidone		0.5%
Chlorobutanol		0.5%
0.9% Sodium chloride solution		qs

1. Calculate the quantity of each ingredient for the total amount to be prepared.
2. Accurately weigh or measure each ingredient.
3. Dissolve all ingredients in the sterile 0.9% sodium chloride solution.
4. Filter through a 0.2 micron filter into a sterile ophthalmic container.
5. Package and label.

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Table 1: Wetting/clarifying agents used for ophthalmic preparations.

Agent	Usual Concentration (%)
Polysorbate 20	1%
Polysorbate 80	1%

Table 2: Common preservatives used in ophthalmic products.

Preservative Name	Usual Conc.	Conc. Range	Max. Conc. %	Incompatibilities
Chlorobutanol		0.5		
Quaternary Ammonium Compounds:	0.01%	0.004 - 0.02%		Soaps, anionic materials, salicylates, nitrates
Benzalkonium chloride			0.013	
Benzethonium chloride			0.01	
Organic Mercurials:		0.001-0.01%		Certain halides with phenylmercuric acetate.
Phenylmercuric acetate			0.004	
Phenylmercuric nitrate			0.004	
Thimerosal			0.01	
Parahydroxybenzoates			0.1%	Adsorption by macromolecules.

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The maximum levels are listed by the FDA Advisory Review Panel on OTC Ophthalmic Drug Products (1979) for direct contact with the eye tissues and not for ocular devices such as contact lens products.

Table 3: Antioxidants used for ophthalmic preparations.

Antioxidant	Usual Concentration (%)
Ethylenediaminetetraacetic acid	0.1%
Sodium bisulfite	0.1%
Sodium metabisulfite	0.1%
Thiourea	0.1%

Table 4: Viscosity increasing agents for ophthalmic preparations.

Agent	Usual Concentration (%)
Hydroxyethylcellulose	0.8
Hydroxypropyl methylcellulose	1.0%
Methylcellulose	2.0%
Polyvinyl alcohol	1.4%
Polyvinylpyrrolidone	1.7%

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