

## **COMPOUNDING OPHTHALMIC LIQUIDS**

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**Goals:** The goals of this article are (1) to review some important theoretical aspects of ophthalmic preparations, and (2) to provide practical guidelines for compounding and dispensing of ophthalmic liquids.

**Objectives:** At the conclusion of this lesson, the reader should be able to:

1. Demonstrate an understanding of the different types of ophthalmic preparations, and excipients used in the preparation of these liquids.
2. Select the appropriate excipients depending on the characteristics of the drug.
3. Exhibit an understanding of the techniques involved in incorporating an active ingredient into an ophthalmic liquid.

### **Introduction**

According to the USP, ophthalmic solutions are sterile solutions, essentially free from foreign particles, suitably compounded and packaged 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. Because of the inherent danger of causing serious eye infection and even loss of eyesight through the use of contaminated ophthalmic solutions, the pharmacist must use the greatest care in preparing these drug preparations.

Ophthalmic solutions should be compounded extemporaneously only if:

1. There are no available commercial product alternatives.
2. The pharmacist possesses the appropriate knowledge and technique.
3. The necessary equipment and supplies are available to make sterile solutions.

### **Desired Properties of Ophthalmic Solutions**

The properties of an ideal ophthalmic solution are described below. Achieving all of these objectives simultaneously is sometimes impossible, and therefore appropriate compromises can be made, or another therapeutic option may be necessary.

A. Sterility and clarity: These are not just desired properties, but absolute requirements for ophthalmic solutions. The preparation and packaging should be done in a sterile environment such as a laminar flow hood or a barrier isolator. A sterile, particle-free solution can be achieved by one of the following methods:

1. Prepare the solution in a manner similar to a parenteral preparation, using aseptic technique with sterile parenteral drug products as the solution ingredients, and packaging the solution in a clean, particle-free, sterile container.
2. Prepare the solution using non-sterile but high-quality ingredients, and filter the solution using a 0.2- or 0.45-micron bacterial filter into a dispensing container that is clean, particle-free, and sterile.
3. If an autoclave is available, terminal steam sterilization can be used. In this case, the solution may be prepared using non-sterile but high-quality ingredients and packaged in an appropriate clean, particle-free container that is stable to the elevated temperature and pressure needed for steam sterilization. The preparation is then autoclaved in the dispensing container. Quality control procedures for steam sterilization must be used, for example, validation of the autoclave cycle through the use of biological and other indicators, as well as the use of monitoring devices that track and record time, temperature and pressure. Since steam sterilization uses elevated temperature and pressure, consideration of drug stability is important before using this method.

B. Preservation: When the solution is dispensed in a multidose container that is to be used over a period of time longer than 24 hours, a preservative must be added to ensure microbiologic safety over the period of use.

C. pH: Although solutions with the same pH as lacrimal fluid (7.4) are ideal, the outer surfaces of the eye tolerate a larger range, 3.5 to 8.5. The normal useful range to prevent corneal damage is 6.5 to 8.5. The final pH of the solution is often a compromise, because many ophthalmic drugs have limited solubility and stability at the desired pH of 7.4. Buffers or pH adjusting agents or vehicles can be added to adjust and stabilize the pH at a desired level. Ophthalmic solutions are ordinarily buffered at the pH of maximum stability of 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 carbon dioxide from the air or from hydroxyl ions from a glass container. Changes in pH can affect the solubility and 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 that when the ophthalmic solution is instilled into the eye, the buffer system of the tears will rapidly bring the pH of the solution back to that of the tears. Low concentrations of buffer salts are used to prepare buffers of low buffer capacity.

D. Isotonicity: Solutions that are isotonic with tears are preferred. An amount equivalent to 0.9% NaCl is ideal for comfort and should be used when possible. The eye can tolerate tonicities within the equivalent range of 0.6-2% NaCl without discomfort. There are times when hypertonic ophthalmic solutions are necessary therapeutically, or when the addition of an auxiliary agent required for reasons of stability supersedes the need for isotonicity. A hypotonic ophthalmic solution will require the addition of a substance (tonicity adjusting agent) to attain the proper tonicity range.

E. Stability: As with all pharmaceutical solutions, ophthalmics must be chemically and physically stable.

F. Therapeutic efficacy: The active ingredient(s) should be present in the most therapeutically effective form. This goal must often be compromised for reasons of solubility or stability of the active ingredient or patient comfort. For example, while many drugs are most active in their undissociated form, they are least soluble in this form. They may also be less stable at pH values that favor the undissociated form.

G. Compatibility with the eye: Ophthalmic solutions should be free of chemicals or agents that cause allergy or toxicity to the sensitive membranes and tissues of the eye. Auxiliary agents, such as preservatives and antioxidants, should be added with care because many patients are sensitive to these substances. Before adding an auxiliary agent, check with the patient about allergies and sensitivities.

### **Active ingredients**

The active ingredients used in ophthalmic liquids are available as pure powder, as sterile powder manufactured for parenteral administration, or as a sterile, parenteral solution of the desired ingredient.

### **Auxiliary agents**

Auxiliary agents added to ophthalmic solutions include buffers, tonicity adjustors, preservatives, antioxidants, and viscosity-inducing agents.

1. Buffers: The most widely used ophthalmic buffer solutions are boric acid vehicle and Sorensen's modified phosphate buffer. The boric acid vehicle is a 1.9% solution of boric acid in purified water or preferably sterile water. It is isotonic with tears. It has a pH of approximately 5 and is useful when extemporaneously compounding ophthalmic solutions of drugs that are most stable at acid pH. This vehicle does not possess large buffer capacity, but it is sufficient to stabilize pH for the short expiratory periods used for compounded solutions, without overwhelming the natural buffers in lacrimal fluid. This is why boric acid solutions are not uncomfortable when instilled in the eye. Boric acid is available as crystals and powder. The crystals are preferred for making boric acid vehicle because they give more crystal-clear solutions than does the powder. Air is often entrapped on the surface of boric acid powder, which causes incomplete dissolution and gives floating aggregates of powder. The second most commonly used buffer solution is the Sorensen's modified phosphate buffer and is used for drugs needing pH values between the range of 6.5-8.0. This buffer uses two stock solutions, one acidic containing  $\text{NaH}_2\text{PO}_4$ , and one basic containing  $\text{Na}_2\text{HPO}_4$ . The formulas for the stock solutions and their respective proportions used to obtain specific pH values are provided in Table 1. Since the buffer mixtures are not isotonic, the table also provides the weight in grams of sodium chloride that must be added to 100 mL of buffer solution to give an isotonic buffer.

Table 1: Sorensen's Modified Phosphate Buffer

mL of NaH <sub>2</sub> PO <sub>4</sub> solution*	mL of Na <sub>2</sub> HPO <sub>4</sub> solution**	pH	NaCl required for isotonicity (g/100mL)
90	10	5.9	0.52
80	20	6.2	0.51
70	30	6.5	0.50
60	40	6.6	0.49
50	50	6.8	0.48
40	60	7.0	0.46
30	70	7.2	0.45
20	80	7.4	0.44
10	90	7.7	0.43
5	95	8.0	0.42

\* 8.006g NaH<sub>2</sub>PO<sub>4</sub>/1000 mL with Purified Water

\*\* 9.473g Na<sub>2</sub>HPO<sub>4</sub>/1000 mL with Purified Water

2. Tonicity adjustor: As indicated above, the buffer solution is convenient to use as the tonicity adjustor. In circumstances when an ophthalmic solution without a buffer is desired, any compatible salt or non-electrolyte that is approved for ophthalmic products may be used. Sodium chloride, sodium nitrate, sodium sulfate, and dextrose are common neutral tonicity adjustors.
3. Preservatives: The USP states the following concerning the use of preservatives in ophthalmic solutions: "Each solution must contain a suitable substance or mixture of substances to prevent the growth of, or to destroy, microorganisms accidentally introduced when the container is opened during use. Where intended for use in surgical procedures, ophthalmic solutions, although they must be sterile, should not contain antibacterial agents, since they may be irritating to the ocular tissues." Because of preservative toxicity, especially following ocular surgery, either unpreserved Sterile Water for Injection or Sterile 0.9% Sodium Chloride Injection should be used as vehicles for ophthalmic drugs. This means that the solution should be discarded after 24 hours because of the danger of contamination by microorganisms. This practice is practical only in a hospital or institutional setting where fresh solution can be furnished every day, so it is useful primarily for inpatients. For ambulatory patients and when hospitalized patients are discharged, it can be assumed that the eye has sufficiently healed so that it is less vulnerable to irritation and toxicity due to preservatives. At this time the solution vehicle can be changed to Bacteriostatic Water for Injection or Bacteriostatic Sodium Chloride Injection. The beyond-use date is then based on the chemical stability of the active ingredient(s). Manufactured artificial tears products contain a preservative(s); they provide another alternative ophthalmic vehicle for ambulatory patients. When using these products for vehicles, consideration must be given to the volume of any added solution so that the preservative in the product is not diluted beyond its effective concentration. Typical preservatives

approved for ophthalmic solutions are listed in Table 2. Benzyl alcohol and the parabens are the preservatives most commonly found in Bacteriostatic Water for Injection and Bacteriostatic Sodium Chloride Injection.

Table 2: Maximum concentrations of preservatives approved for use in ophthalmic products.

<b>Antimicrobial Preservative</b>	<b>Maximum Concentration</b>
Benzalkonium chloride	0.013%
Benzethonium chloride	0.01%
Chlorobutanol	0.5%
Phenylmercuric acetate	0.004%
Phenylmercuric nitrate	0.004%
Thimerosal	0.01%

4. Antioxidants: Certain active ingredient(s) may be susceptible to oxidative degradation. Literature references and compounding monographs can be consulted for information on individual drugs. If oxidation is a problem, an antioxidant is recommended. Table 3 provides a listing of approved antioxidants for use in nonprescription ophthalmic products. Sodium metabisulfite is official in the USP. Sodium bisulfite is not official in the USP, but it is available as FCC (Food Chemical Codex) grade, which is acceptable for use in drug preparations. Disodium edetate is technically not an antioxidant, but a chelator of heavy metal ions. It serves as an antioxidant for drugs that have their oxidation catalyzed by heavy metals.

Table 3: Maximum concentrations of antioxidants approved for use in ophthalmic products.

<b>Antioxidant</b>	<b>Maximum Concentration</b>
Sodium bisulfite	0.1%
Sodium metabisulfite	0.1%
Thiourea	0.1%
Disodium edetate	0.1%

5. 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. If methylcellulose is autoclaved, it will come out of solution. However, it can be redispersed after cooling, especially if placed in a refrigerator. 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 enhancing additives are listed in Table 4.

Table 4: Typical concentrations of viscosity-enhancing agents approved for use in ophthalmic liquids.

Viscosity agent	Typical concentration
Polyvinyl alcohol	1.4%
Polyvinylpyrrolidone	1.7%
Methylcellulose	2.0%
Hydroxypropyl methylcellulose	1.0%
Hydroxyethylcellulose	0.8%

6. **Clarity:** Ophthalmic solutions must be free from foreign particles, and this is generally accomplished by filtration. The filtration process also helps to achieve clarity of the solution. Table 5 contains a list of suitable clarifying agents. These agents are surfactants that improve aqueous drug solubility and are compatible with vehicles used to prepare ophthalmic liquids.

Table 5: Wetting/clarifying agents approved for use in ophthalmic preparations.

Agent	Usual concentration
Polysorbate 20	1.0%
Polysorbate 80	1.0%

## Preparation Methods/Techniques

### Solutions

1. Accurately weigh/measure each of the ingredients.
2. Dissolve the ingredients in about 3/4<sup>th</sup> 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. Dissolve/mix the ingredients in about 3/4<sup>th</sup> 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.

### **Suspensions (alternate method)**

1. Accurately weigh/measure each of the ingredients.
2. Sterilize each of the ingredients by a suitable method.
3. Dissolve/mix the ingredients in about  $3/4^{\text{th}}$  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.

### **Packaging/Storage/Labeling**

Packaging of ophthalmic solutions is appropriately done in sterile dropper bottles, or individual doses can be placed in sterile syringes, without needles. 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 are not later than 14 days, when stored at refrigerated temperatures, for products prepared from ingredients in solid form when the stability of the ingredients in the formulation is not known. With sterile preparations like ophthalmic solutions, an even more conservative approach is advisable. A beyond-use date of 1 to 2 weeks is a reasonable guideline for relatively stable drugs in sterile, preserved solutions. For non-aqueous liquids, the beyond-use recommendation is not later than 25% of the time remaining until the product's expiration date, or six months, whichever is earlier. These beyond-use recommendations can be extended if there is supporting valid scientific stability information.

Unpreserved ophthalmics should be dispensed in single-dose quantities and should be treated essentially like unpreserved parenteral products. If possible they should be made immediately before use. If use is delayed, they may be stored under refrigeration and warmed to room temperature just before use. A 24-hour dating is recommended for unpreserved ophthalmic solutions.

### **Incompatibilities**

Zinc salts can form insoluble hydroxides at a pH above 6.4, so a Boric Acid Solution vehicle may be selected. It 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.

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 agglomerates or caking.

### **Example Vehicles**

#### Isotonic Sodium Chloride Solution

Sodium Chloride USP		0.9g
Benzalkonium Chloride		1:10,000
Sterile Water for Injection	qs	100 mL

#### Boric Acid Solution

Boric Acid USP		1.9g
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	

#### **Preparation**

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.

### **Suggested Readings**

1. 'A practical guide to contemporary pharmacy practice' by Judith E. Thompson, Second Edition. Lippincott, Williams & Wilkins. 2004
2. 'Pharmaceutical Dosage Forms and Drug Delivery Systems' by Howard C. Ansel, Nicholas G. Popovich, and Loyd V. Allen, Jr. Eighth Edition. Lippincott, Williams & Wilkins. 2005.
3. 'Trissel's Stability of Compounded Formulations' by Lawrence A. Trissel, Fourth Edition, American Pharmacists Association, 2009.



## **Continuing Education Quiz**

**1. All the following are characteristics of an ideal ophthalmic solution, EXCEPT:**

- a. It must be isotonic
- b. It is not required to be sterile
- c. It should have a mild buffer capacity
- d. It should have a pH in the range of 6.5-8.5

**2. Tonicity adjusters used in ophthalmic solutions include all of the following, EXCEPT:**

- a. Benzalkonium chloride
- b. Sodium nitrate
- c. Dextrose
- d. Sodium chloride

**3. Which of the following is NOT an antimicrobial preservative used in ophthalmic products?**

- a. Chlorobutanol
- b. Phenylmercuric acetate
- c. Thimerosal
- d. Sodium lauryl sulfate

**4. Ophthalmic solutions may contain all of the following excipients, EXCEPT:**

- a. Antioxidants
- b. Buffers
- c. Ethyl alcohol
- d. Clarifying agents

**5. Which of the following statements is FALSE?**

- a. The eye can tolerate tonicities within the equivalent range of 0.6-2% NaCl without discomfort.
- b. Lacrimal fluids possess natural buffers that maintain a pH of 7.4.
- c. The outer surfaces of the eye can tolerate a pH range of 3.5 to 8.5.
- d. Changes in pH have no effect on drug solubility and stability.

**6. Antioxidants used in ophthalmic solutions include all of the following, EXCEPT:**

- a. Boric acid
- b. Sodium bisulfite
- c. Thiourea
- d. Sodium metabisulfite

**7. Identify the FALSE statement about ophthalmic liquids from the following:**

- a. Ophthalmic liquids must not be autoclaved.
- b. An increase in the viscosity of ophthalmic liquids will result in a longer residence time in the eye, providing increased drug absorption.
- c. Viscosity enhancers should not affect solution clarity.

- d. If methylcellulose is autoclaved, it will come out of solution. However, it can be redispersed after cooling, especially if placed in a refrigerator.

**8. Viscosity-enhancing agents used in ophthalmic solutions include all of the following, EXCEPT:**

- a. Polyvinyl alcohol
- b. Hydroxyethylcellulose
- c. Disodium edetate
- d. Polyvinylpyrrolidone

**9. Select the FALSE statement from the following:**

- a. A beyond-use date of 1 to 2 weeks is a reasonable guideline for relatively stable drugs in sterile, preserved ophthalmic solutions.
- b. Ophthalmic solutions intended for use in surgical procedures must contain antibacterial preservatives.
- c. Unpreserved ophthalmics should be dispensed in single-dose quantities.
- d. A 24-hour beyond-use dating is recommended for unpreserved ophthalmic solutions.

**10. All of the following statements about incompatibilities in ophthalmic liquids are true, EXCEPT:**

- a. Zinc salts can form insoluble hydroxides at a pH above 6.4, so Boric Acid Solution vehicle may be selected.
- b. Nitrates and salicylates are incompatible with solutions of benzalkonium chloride.
- c. Sodium chloride cannot be used to adjust the tonicity of silver nitrate solutions.
- d. Polysorbate 80 is not compatible with Sterile Water for Injection.

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