

The Art, Science, and Technology of Pharmaceutical Compounding

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Ophthalmic, Otic, and Nasal Preparations

In this chapter, compounded products are grouped by route of administration rather than by dosage forms. For that reason, the chapter is divided into three major sections: ophthalmic, otic, and nasal preparations.

Ophthalmic Preparations

Definitions/Types

Ophthalmic solutions are sterile, free from foreign particles, and prepared especially for instillation into the eye. *Ophthalmic suspensions* are sterile liquid preparations that contain solid particles in a vehicle suitable for instillation into the eye. *Ophthalmic ointments* are sterile preparations designed for application to the eye. They have an ointment base and may or may not include an active drug.

Historical Use

One of the early treatments of eye conditions with a liquid involved the use of the juice of a liver. This preparation was one of the earlier observations that applying substances topically to the eye was effective. In this case, the vitamin A content of the juice was effective in treating the condition. Throughout history various plant extracts have also been prepared and used for eye conditions. Today's vehicles for ophthalmic liquids include primarily sterile, buffered aqueous systems that contain preservatives.

"Eye salves" were prepared during the period of the early Roman Empire by "medici ocularii," or men who specialized in the preparation of such salves. One such product was described on a piece of green statite as containing "crocus of Lucius Vallatinus for affectations of the eyes." Evidence exists that ophthalmic ointments were used throughout the Roman Empire and even in such outlying areas as Scotland. Ointments developed later used oils and fats as their vehicles. More recently, the petrolatums were used as vehicles for these ophthalmic preparations.

Composition

In addition to the active drugs, ophthalmic preparations contain a number of excipients, including vehicles, buffers, preservatives, tonicity-adjusting agents, antioxidants, and viscosity enhancers. Ingredients used in the formulation process must be nonirritating to and compatible with the eyes.

Applications

Ophthalmic preparations are used to treat allergies, bacterial and viral infections, glaucoma, and numerous other eye conditions. The eye is constantly exposed to the atmosphere, dust, pollutants, allergens, bacteria, and foreign bodies. When the eye's natural defensive mechanisms are compromised or overcome, an ophthalmic product, in either a solution, suspension, or ointment form, may be indicated. Solutions are used most often to deliver a drug to the eye. Although solutions have a relatively short duration of action, they spread easily over the globe and cover well. Suspensions have a slightly longer duration of action because the particles will usually settle in the lower conjunctival sac and release the drug as the particles dissolve. Ointments have an even longer duration of action. The ointment spreads over the eye and into the conjunctival sac. The active drug is released slowly as the vehicle is slowly removed from the eye.

Preparation

All preparation must be done in a clean air environment by a qualified aseptic compounding pharmacist. The pharmacist must ensure that all the ingredients are of the highest grade that can be reasonably obtained. The box on page 221 lists the steps involved in preparing ophthalmic solutions, suspensions, and ointments.

Physicochemical Considerations

In preparing ophthalmic solutions, one must consider the general physicochemical parameters: clarity, tonicity, pH/buffers, and sterility. The addition of excipients such as preservatives, antioxidants, and viscosity enhancers, as well as potential incompatibilities between these excipients and active drugs, should also be considered.

Clarity

✓ Ophthalmic solutions must be free from foreign particles. Filtration is generally used to remove these particles and to achieve clarity of the solution. Polysorbate 20 and Polysorbate 80, in a maximum concentration of 1%, can also be used to achieve clarity.

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 virtue of the high concentration required of the drug substance. Others will be hypotonic and will require adjustment to attain the proper tonicity range; sodium chloride, boric acid, and dextrose are commonly used for this purpose. The ideal tonicity is 300 mOsm/L; however, a range of 200 to 600 mOsm/L is 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

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Preparation of Ophthalmic Products

Solutions

1. Accurately weigh or measure each ingredient.
2. Dissolve the ingredients in about three fourths of the quantity of sterile water for injection and mix well.
3. Add sufficient sterile water for injection to volume and mix well.
4. Take a sample of the solution and determine the pH, clarity, and other quality control factors.
5. Filter through a sterile 0.2 μ filter into a sterile ophthalmic container.
6. Package and label.
7. If a large number of solutions are to be prepared, select a random sample to be assayed and checked for sterility.

Suspensions (Method 1)

1. Accurately weigh or measure each ingredient.
2. Dissolve the ingredients in about three fourths of the quantity of sterile water for injection and mix well.
3. Add sufficient sterile water for injection to volume and mix well.
4. Take a sample of the solution and determine the pH and other quality control factors.
5. Package in a suitable container for autoclaving.
6. Autoclave, cool, and label.
7. If a large number of suspensions are to be prepared, select a random sample to be assayed and checked for sterility.

Suspensions (Method 2)

1. Accurately weigh or measure each ingredient.
2. Sterilize each ingredient by a suitable method.
3. Dissolve the ingredients in about three fourths of the quantity of sterile water for injection and mix well.
4. Add sufficient sterile water for injection to volume and mix well.
5. Take a sample of the suspension and determine the pH and other quality control factors.
6. Package and label.
7. If a large number of solutions are to be prepared, select a random sample to be assayed and checked for sterility.

Ointments

1. Accurately weigh or measure each ingredient.
2. Sterilize each ingredient by a suitable method.
3. Mix the ingredients with the sterile vehicle.
4. Take a sample of the ointment and determine the quality control factors.
5. Package and label.
6. If a large number of ointments are to be prepared, select a random sample to be assayed and checked for sterility.

pH that may occur during the storage life of the drug; this change can result from carbon dioxide absorbed from the air or from hydroxyl ions absorbed from a glass container. Changes in pH can affect the solubility and the stability of drugs; consequently, it is important to minimize such fluctuations. The buffer system should be designed so that it maintains the pH throughout the expected shelf life of the

product, but has a buffer capacity that is low enough that when 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. Thus, the pharmacist should use a concentration of buffer salt that is effective but as low as possible. Generally, a buffer capacity of less than 0.05 is desired; pH in the range of 4 to 8 is considered optimum.

Sterility

Ophthalmic solutions must be sterile. Sterility is best achieved through sterile filtration, which involves using a sterile membrane filter of 0.45 μ or 0.2 μ pore size and filtering into a sterile container. Other methods of sterilizing ingredients or components of ophthalmics include dry heat; steam under pressure, that is, autoclaving (see Figure 20-1), and gas sterilization with ethylene oxide.

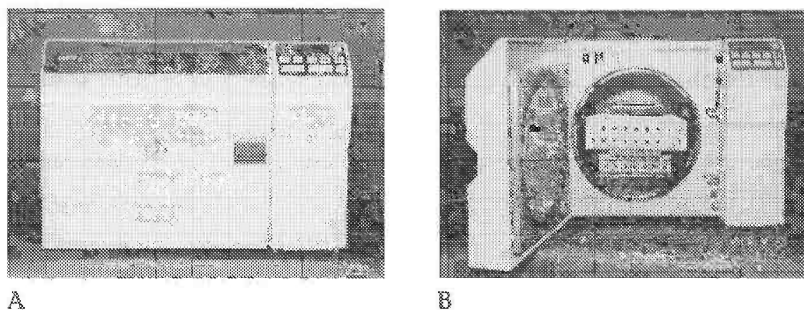


Figure 20-1. Microprocessor-controlled sterilizer/autoclave: A, exterior view; B, interior view.

Other Excipients

Since most ophthalmic solutions and suspensions are prepared in multi-use containers, they must be preserved. The preservative used must be compatible with the active drug as well as with all the other excipients in the product. Common preservatives for ophthalmic products are shown in Table 20-1.

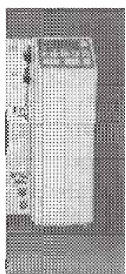
Antioxidants may be required for selected active drug ingredients. Table 20-2 lists a number of antioxidants that can be used in ophthalmic preparations.

If the viscosity of an ophthalmic product increases, the product will remain in the eye longer and thereby allow more time for drug absorption and effect. To increase the viscosity, viscosity enhancers are used, the most common of which is methylcellulose, 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. Other good choices are hydroxypropylmethylcellulose or methylcellulose in the range of 0.5% to 1%. Also acceptable is polyvinyl alcohol in a range of 0.5% to 1.5% weight/volume. Solution viscosity ranging from 25 to 50 cps is common. With all of these enhancers, however, it is important that the clarity of the solution be maintained. Additives that increase viscosity are shown in Table 20-3.

Ophthalmic ointments must be prepared so that they do not irritate the eye, permit diffusion of the drug, and retain the activity of the drug for a reasonable period of time when stored properly. The base primarily used for ophthalmic ointments is

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Table 20-1. Preservatives Commonly Used in Ophthalmic, Otic, and Nasal 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

*The FDA Advisory Review Panel on OTC Ophthalmic Drug Products (1979) lists these concentrations for preparations that have direct contact with the eye tissues and not for ocular devices such as contact lens products.

Table 20-2. Antioxidants Used for Ophthalmic and Nasal Preparations

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

Table 20-3. Viscosity Enhancers for Ophthalmic Preparations

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

white petrolatum. Aqueous solutions of the drug can be incorporated by using an absorption base, as long as it does not irritate the eye. One example is anhydrous lanolin mixed with white petrolatum. The pharmacist must be aware that surfactants

used to make absorption bases may cause eye irritation. Powders incorporated in the preparation must be micronized and sterilized to ensure that the final product is not gritty and thus nonirritating.

The size of the particles in an ophthalmic suspension must be small enough that they do not irritate and/or scratch the cornea. The micronized form of the drug is required. Ophthalmic suspensions must be free from agglomeration or caking.

Incompatibilities

Because zinc salts can form insoluble hydroxides at a pH above 6.4, a boric acid solution vehicle may be used. Boric acid solution also has a lower pH (about pH 5) and a 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 because silver chloride would precipitate. Instead, sodium nitrate should be used to adjust the tonicity, and phenylmercuric nitrate can be used as the preservative in this situation.

Quality Control

The compounding pharmacist should follow standard quality control procedures. These include checking the sterility, clarity, appearance, pH, and volume/weight. Sterility can be checked by plating a sample of the product on an agar plate and checking for microbial growth. If this procedure is not feasible, product samples can be sent to a laboratory for testing.

Packaging/Storage/Labeling

Ophthalmic solutions should be packaged in sterile dropper bottles. Individual doses can also be placed in sterile syringes, without needles. Generally, these preparations should be stored at either room or refrigerated temperatures. They should not be frozen. Ophthalmic preparations should be labeled "For the Eye," "Do Not Touch the Eye or Eyelid," "Store as Indicated," and "Dispose after [appropriate date]."

Stability

Beyond-use dates for water-containing formulations are no later than 14 days, when stored at cold temperatures, for products prepared from ingredients in solid form. If nonaqueous liquids are prepared using a manufactured product, the beyond-use recommendation is no later than 25% of the time remaining on the product's expiration date or 6 months, whichever is earlier. For all others, the recommended beyond-use date is the intended duration of therapy or 30 days, whichever is earlier. These beyond-use recommendations can be extended if valid scientific information is available to support the stability of the product, as discussed in Chapter 4, "Stability of Compounded Products."

Patient Counseling

Patients should be instructed on how to administer drops or ointments to the eye. Specifically, they should be cautioned not to allow the tip of the dropper or ointment tube to touch any part of the eye. They should also be instructed to allow the drug to fall freely into the eye and not to allow the drug to touch the eye and then be drawn back into the bottle.

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Sample Vehicles

The steps listed for solutions in the box Preparation of Ophthalmic Products should be followed to prepare these vehicles.



Isotonic Sodium Chloride Solution

Sodium chloride USP	0.9 g
Benzalkonium chloride	1:10,000
Sterile water for injection	qs 100 mL

Three buffer solutions have been suggested for certain drugs when they are prepared as ophthalmic solutions. These drugs have been divided into three classes and are listed with the recommended buffer solution for that class.

The following drugs in Class IA can be placed in Buffer Solution IA, which has a pH of about 5:

- Cocaine,
- Dibucaine (Nupercaine),
- Neostigmine (Prostigmin),
- Phenacaine (Holocaine),
- Piperocaine (Metycaine),
- Procaine,
- Tetracaine (Pontocaine), and
- Zinc.



Buffer Solution IA

Boric acid USP	1.9 g
Benzalkonium chloride	1:10,000
Sterile water for injection	qs 100 mL

Some drugs may be incompatible with Buffer Solution IA because of an incompatibility with benzalkonium chloride. Buffer Solution IB contains a different preservative, phenylmercuric nitrate. Sodium sulfite has been added to prevent discoloration/oxidation of some of the drugs in this category. Drugs that are incompatible in Buffer Solution IA but can be prepared using Buffer Solution IB include the following Class IB drugs:

- Physostigmine,
- Phenylephrine, and
- Epinephrine.



Buffer Solution IB

Boric acid USP	1.9 g
Sodium sulfite, anhydrous	0.1 g
Phenylmercuric nitrate	1:50,000
Sterile water for injection	qs 100 mL

Drugs in Class II that can be prepared in Buffer Solution II include the following:

- Atropine,
- Ephedrine,
- Homatropine, and
- Pilocarpine.



Buffer Solution II

Sodium acid phosphate, anhydrous	0.560 g
Disodium phosphate, anhydrous	0.284 g
Sodium chloride USP	0.5 g
Disodium edetate	0.1 g
Benzalkonium chloride	1:10,000
Sterile water for injection	qs 100 mL

Sample Formulations



Artificial Tears Solution

Polyvinyl alcohol	1.5%
Povidone	0.5%
Chlorobutanol	0.5%
0.9% Sodium chloride solution	qs

1. Calculate the quantity of each ingredient required for the prescription.
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 μ filter into a sterile ophthalmic container.
5. Package and label.



Cocaine Hydrochloride Ophthalmic Solution

Cocaine hydrochloride	5 g
Ethylenediaminetetraacetic acid	10 mg
Benzalkonium chloride	10 mg
Sterile 0.9% sodium chloride solution	qs 100 mL

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R_x Cocaine Hydrochloride Ophthalmic Solution (cont.)

1. Calculate the quantity of each ingredient required for the prescription.
2. Accurately weigh or measure each ingredient.
3. Dissolve the cocaine hydrochloride, ethylenediaminetetraacetic acid, and benzalkonium chloride in sufficient sterile 0.9% sodium chloride solution to make 100 mL.
4. Filter through a sterile 0.2 μ filter into a sterile container.
5. Package and label.

R_x Cyclosporine Ophthalmic Solution

Cyclosporine	2%
Corn oil or olive oil	qs

1. Calculate the quantity of each ingredient required for the prescription.
2. Accurately weigh or measure each ingredient.
3. Use alcohol to clean the container to be used for mixing the oral cyclosporine 10% solution and oil.
4. Clean a commercial container of cyclosporine 10% solution with alcohol; open the container and place it in a laminar flow hood for about 24 hours to allow the alcohol to evaporate.
5. Mix four volumes of corn oil or olive oil with one volume of the 10% cyclosporine oral solution; mix thoroughly in the previously cleaned container.
6. Filter through a 0.2 μ filter into a sterile, dry ophthalmic container.
7. Package and label.

R_x Ophthalmic Decongestant Solution

Phenylephrine hydrochloride	0.125%
Polyvinyl alcohol	1.4%
Disodium edetate	0.05%
Sodium acetate	0.1%
Monobasic sodium phosphate	0.1%
Dibasic sodium phosphate	0.05%
Sodium thiosulfate	0.1%
Sterile water for injection	qs 100%

1. Calculate the quantity of each ingredient required for the prescription.
2. Accurately weigh or measure each ingredient.
3. Dissolve all the ingredients in sterile water for injection.
4. Filter through a sterile 0.2 μ filter into a sterile container.
5. Package and label.

Rx Ophthalmic Lubricant

White petrolatum	55%
Mineral oil	41.5%
Lanolin alcohol	2%
0.9% Sodium chloride injection	1.5%

1. Calculate the quantity of each ingredient required for the prescription.
2. Accurately weigh or measure each ingredient.
3. Mix the white petrolatum, mineral oil, and lanolin alcohol together, using a water bath.
4. Sterilize the mixture with dry heat.
5. Using aseptic technique, cool the sterile mixture in a laminar flow hood; then incorporate the sterile 0.9% sodium chloride injection and mix.
6. Package in sterile containers.

Rx Tobramycin Fortified Ophthalmic Solution

Tobramycin ophthalmic solution	5 mL
Tobramycin injection, 80 mg/2mL	1 mL

1. Calculate the quantity of each ingredient required for the prescription.
2. Prepare the product using aseptic technique.
3. Accurately measure each ingredient.
4. Mix well, package, and label.

Rx Acetylcysteine 10% Ophthalmic Solution

Acetylcysteine	10%	2 g (10 mL of a 20% solution)
Disodium edetate	0.025%	5 mg
Chlorobutanol	0.5%	100 mg
Artificial tears solution	qs	20 mL

(Note: Prepare in a clean air environment.)

1. Calculate the quantity of each ingredient required for the prescription.
2. Accurately weigh or measure each ingredient.
3. Place the chlorobutanol in a clean, previously sterilized beaker.
4. Add 9 mL of artificial tears solution.
5. Cover and stir (with a magnetic mixer with stir bar) until dissolved.
6. Add the disodium edetate to the solution.
7. Add 10 mL of 20% acetylcysteine oral inhalation solution.
8. Filter the solution through a 0.2 μ filter into a sterile ophthalmic container.
9. Package and label.

R_x Tropicamide-Hydroxyamphetamine Hydrobromide Ophthalmic Solution

Tropicamide	0.25%	250 mg
Hydroxyamphetamine hydrobromide	1%	1 g
Benzalkonium chloride	0.005%	5 mg
Disodium edetate	0.5%	500 mg
Sodium chloride	—	490 mg
Sodium hydroxide or Hydrochloric acid to adjust pH to 4.2 to 5.8		
Sterile water for injection	qs 100%	100 mL

1. Calculate the quantity of each ingredient required for the prescription.
2. Accurately weigh or measure each ingredient.
3. Dissolve the solid ingredients in approximately 50 mL of sterile water for injection.
4. Add the benzalkonium chloride dilution to the solution and mix well.
5. Add sufficient water to make about 90 mL and mix well.
6. Adjust the pH to between 4.2 and 5.8, using the sodium hydroxide or hydrochloric acid.
7. Add sufficient sterile water for injection to make 100 mL.
8. Filter through a 0.2 μ filter into sterile containers.
9. Package and label.

The benzalkonium chloride for this prescription can be prepared as follows:

1. Accurately measure 1 mL of 50% benzalkonium chloride solution.
2. Place in a 100-mL graduated cylinder.
3. Add sufficient sterile water for injection to make 100 mL and mix well.
4. Remove 1 mL of the solution, which contains 5 mg of benzalkonium chloride, and add it to the solution containing the active drug.

Otic Preparations

Definitions/Types

Otic preparations can be in liquid, ointment, or powder dosage forms. Both *otic solutions* and *suspensions*, the liquid dosage forms, are prepared for instillation into the ear. Solutions are liquid preparations in which all ingredients are dissolved, while suspensions are liquid preparations containing insoluble materials. Solutions are also used for irrigating the ear. *Otic ointments* are semisolid preparations that are applied to the exterior of the ear. *Insufflations* are preparations made of finely divided powder that are administered to the ear canal. Insufflating a powder into the ear canal is not too common because the ear lacks fluids and a powder-wax buildup may occur.

Historical Use

Throughout history medications have been administered to the ear for a local effect. Early otic preparations were applied by soaking materials, such as cloth, wood, or plants, in various oils or extracts from plants or animals and then placing the impregnated materials in the ear. A more recent method of applying otic preparations involves placing a liquid in the ear and inserting a cotton plug to keep the medication from draining out of the ear. This method is still used today, along with the use of ear irrigants, which clean debris from the ear. This debris is the cause of many otic infections.

Applications

Otic irrigating solutions, which may consist of surfactants, weak sodium bicarbonate, boric acid (0.5%–1%), or aluminum acetate solutions, may be warmed to about 37°C before instillation into the ear. These irrigating solutions may be used to remove ear wax, purulent discharges of infection, and foreign bodies from the ear canal.

Otic suspensions can be used when a long duration of drug effect is desired or when the drug is not soluble in the vehicles commonly used in otic preparations.

Fine powders used as insufflations may contain an antibacterial and/or an antifungal agent that will create a repository for the drug. A small rubber or plastic bulb insufflator (powder blower, puffer) can be used to blow, or insufflate, the powder into the ear.

Otic ointments are seldom used. Any ointment base can be used in their preparation, however, and they may include antibacterial, antifungal, or corticosteroid ingredients. These ointments are applied directly to the exterior portions of the ear.

Composition

Categories of medications commonly used in the ear include local anesthetics, cleansing agents (peroxides), anti-infectives, and antifungals. Also included are liquids for cleaning, warming, or drying the external ear and for removing any fluids that may be entrapped by a local waxy buildup.

Vehicles used most often in otic preparations are glycerin, propylene glycol, and the lower molecular weight polyethylene glycols (PEGs), especially PEG 300. These vehicles are viscous and will adhere to the ear canal. Water and alcohol (ethanol and isopropyl) can be used as vehicles and solvents for some medications; however, they are used primarily for irrigation, since one of the therapeutic aims of these preparations is to keep the ear canal dry to minimize bacterial/fungal growth. Alcohol can be used full strength. Vegetable oils, especially olive oil, are also good vehicles. Mineral oil has been used as a vehicle for some antibiotics and anti-inflammatory medications. Otic ointments primarily contain petrolatum as a vehicle, whereas otic powders may contain talc or lactose as a vehicle.

Preparation

The method of formulating otic preparations is similar for all four dosage forms. The box on the next page lists the specific steps involved in preparing otic solutions, suspensions, and ointments and powders.

Physicochemical Considerations

Physicochemical considerations in developing otic preparations include solubility, viscosity, tonicity, surfactant properties, and preservatives. Although sterility is not generally a consideration, the products need to be "clean."

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Preparation of Otic Products

Solutions

1. Accurately weigh or measure each of the ingredients.
2. Dissolve the ingredients in about three fourths of the quantity of the vehicle and mix well.
3. Add sufficient vehicle to volume and mix well.
4. Take a sample of the solution and determine the pH, clarity, and other quality control factors.
5. Package and label.

Suspensions

1. Accurately weigh or measure each of the ingredients.
2. Dissolve or mix the ingredients in about three fourths of the quantity of the vehicle and mix well.
3. Add sufficient vehicle to volume and mix well.
4. Take a sample of the suspension and determine the pH, and other quality control factors.
5. Package in a suitable container.
6. Label.

Ointments

1. Accurately weigh or measure each of the ingredients.
2. Mix each of the ingredients with the vehicle.
3. Take a sample of the ointment and determine the quality control factors.
4. Package and label.

Powders

1. Accurately weigh or measure each of the ingredients.
2. Geometrically mix the powders together, starting with the powders present in the smallest quantity.
3. Take a sample of the powder and determine the quality control factors.
4. Package and label.

Many drugs are soluble in the vehicles commonly used in these preparations. If a drug is insoluble in these vehicles, the preparation can be prepared as a suspension. Because most of these vehicles are relatively viscous agents, the addition of suspending agents may not be necessary.

The viscosity of the preparation is important in keeping the medication in the ear canal. If the preparation is too thin, the medication will drain out of the ear. On the other hand, if the medication is too thick, it may not reach the inner recesses of the ear.

Hygroscopicity and tonicity are important in the product's ability to aid in withdrawing fluids from the immediate area of the ear. If the product is hypertonic, some fluid may be withdrawn from the ear, thereby releasing some of the pressure. If the product is hypotonic, however, some fluid may flow into the area.

Because many ear conditions are related to the difficulty in cleaning the ear, the presence of a surfactant in the preparation helps the medication spread out and aids in breaking up ear wax. This action makes it easier to remove any foreign material.

Many otic preparations are self-preserving because of the high concentration of glycerin, propylene glycol, and the like. If these agents are not present, it may be wise to add a preservative to minimize the chance of introducing bacteria that might grow in an unpreserved product.

Quality Control

The compounding pharmacist should follow standard quality control procedures. These include checking the volume/weight, pH, viscosity, appearance, and odor of these products.

Packaging/Storage/Labeling

Otic preparations should be packaged in dropper containers (see Figure 20-2), puffers, or tubes appropriate for the product and method of administration. Generally, otic preparations should be stored at either room or refrigerated temperatures. They should not be frozen. These preparations should be labeled "For the Ear," "Discard after [appropriate date]," and "Use Only as Directed."

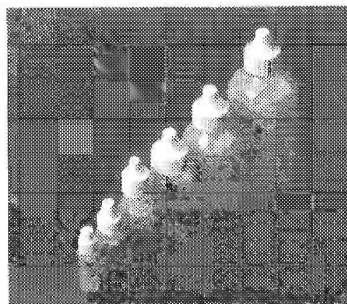


Figure 20-2. Dropper containers in various sizes (3 mL, 7 mL, 15 mL, 30 mL, 60 mL, 125 mL).

Stability

Beyond-use dates for water-containing formulations are no later than 14 days, when stored at cold temperatures, for products prepared from ingredients in solid form. If nonaqueous liquids are prepared using a manufactured product, the beyond-use recommendation is no later than 25% of the time remaining on the product's expiration date or 6 months, whichever is earlier. For all other products, the beyond-use recommendation is the intended duration of therapy or 30 days, whichever is earlier. These beyond-use recommendations can be extended if there is valid scientific information to support the stability of the product, as discussed in Chapter 4, "Stability of Compounded Products."

Patient Counseling

Patients should be instructed on how to apply drops to the ear from dropper bottles. They should also be told to place a cotton or gauze pad in the ear to keep the liquid from escaping.

Sample Formulation



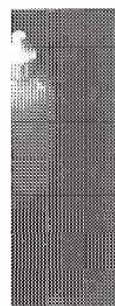
Benzocaine Otic Solution

Benzocaine	200 mg
Glycerin	qs 15 mL

1. Calculate the quantity of each ingredient required for the prescription.
2. Accurately weigh or measure each ingredient.
3. Dissolve the benzocaine in sufficient glycerin to make 15 mL of solution.
4. Package and label.

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Nasal Preparations

Definitions

Nasal solutions are solutions prepared for nasal administration either as drops or as sprays. *Nasal suspensions* are liquid preparations containing insoluble materials for nasal administration. *Nasal gels* (see Chapter 19, "Gels") and *ointments* are semisolid preparations prepared for nasal application that can be for either local or systemic use. The gels are generally water soluble.

Historical Use

"Collunaria" is the term for early nasal preparations that originally contained various oils as the vehicles. As it became apparent that spraying or dropping oil into the nose could be harmful, there was a shift to using aqueous vehicles. Aqueous vehicles with some modifications are used today in these preparations. In recent years, the trend in vehicle preparation has been toward developing isotonic, preserved vehicles that do not interfere with the action of nasal cilia.

Applications

A number of drug substances can be prepared as nasal solutions to be administered either as drops or as sprays; other dosage forms include nasal gels, jellies, or ointments. Some drugs are sufficiently volatile that they can be carried into the nose through an inhaler.

Composition

In addition to the active drugs, nasal preparations contain a number of excipients, including vehicles, buffers, preservatives, tonicity-adjusting agents, gelling agents, and possibly antioxidants. Ingredients used in the formulation process must be nonirritating and compatible with the nose.

Preparation

The methods used to formulate the four dosage forms of nasal preparations are similar. The box below lists the steps to be followed when preparing nasal solutions, suspensions, ointments, and gels.

Preparation of Nasal Products

Solutions

1. Accurately weigh or measure each of the ingredients.
2. Dissolve the ingredients in about three fourths of the quantity of sterile water for injection and mix well.
3. Add sufficient sterile water for injection to volume and mix well.
4. Take a sample of the solution and determine the pH, clarity, and other quality control factors.
5. Filter through a sterile 0.2 μ filter into a sterile nasal container.
6. Package and label.
7. If a large number of solutions are to be prepared, select a random sample to be assayed and checked for sterility.

Preparation of Nasal Products (cont.)**Suspensions (Method 1)**

1. Accurately weigh or measure each ingredient.
2. Dissolve/mix the ingredients in about three fourths of the quantity of sterile water for injection and mix well.
3. Add sufficient sterile water for injection to volume and mix well.
4. Take a sample of the suspension and determine the pH and other quality control factors.
5. Package in a suitable container for autoclaving.
6. Autoclave, cool, and label.
7. If a large number of suspensions are to be prepared, select a random sample to be assayed and checked for sterility.

Suspensions (Method 2)

1. Accurately weigh or measure each ingredient.
2. Sterilize each ingredient using a suitable method.
3. Dissolve/mix the ingredients in about three fourths of the quantity of sterile water for injection and mix well.
4. Add sufficient sterile water for injection to volume and mix well.
5. Take a sample of the suspension and determine the pH and other quality control factors.
6. Package and label.
7. If a large number of suspensions are to be prepared, select a random sample to be assayed and checked for sterility.

Ointments

1. Accurately weigh or measure each ingredient.
2. Sterilize each ingredient using a suitable method.
3. Mix each ingredient with the sterile vehicle.
4. Take a sample of the ointment and determine the quality control factors.
5. Package and label.
6. If a large number of ointments are to be prepared, select a random sample to be assayed and checked for sterility.

Gels

1. Accurately weigh or measure each ingredient.
2. Dissolve the ingredients in about three fourths of the quantity of sterile water for injection and mix well.
3. Filter through a sterile 0.2 μ filter into a sterile container.
4. Add the gelling agent (previously sterilized) and mix well.
5. Add sufficient sterile water for injection to volume/weight and mix well.
6. Take a sample of the gel and determine the pH, clarity, and other quality control factors.
7. Package and label. (Note: Sterile 1-mL syringes that are preloaded with individual doses work well.)
8. If a large number of gels are to be prepared, select a random sample to be assayed and checked for sterility.

Physicochemical Considerations

A vehicle for a nasal solution would have a pH in the range of 5.5 to 7.5 and a mild buffer capacity. It would be isotonic, stable, preserved, and compatible with normal ciliary motion and ionic constituents of nasal secretions, as well as with the active ingredient. It would not modify the normal mucus viscosity.

pH and Buffering

Nasal preparations 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 that may occur during the storage life of the drug. This change in pH can affect the solubility and stability of drugs; consequently, it is important to minimize such fluctuations. The buffer system should be designed to maintain the pH throughout the expected shelf life of the product, but with a low buffer capacity. Generally, pH in the range of 4 to 8 is considered optimum. pH and buffer-phosphate buffer systems are usually compatible with most nasal medications.

Tonicity Adjustment

The preferred agents for adjusting the tonicity of nasal solutions are sodium chloride and dextrose. Severely hypertonic solutions should be avoided. Nasal fluid has an isotonicity value similar to a 0.9% sodium chloride solution. If the isotonicity is beyond the proper range, the nasal ciliary movement may slow or even stop. Tonicity values ranging from 0.6% to 1.8% sodium chloride equivalency are generally acceptable. If the solution of the active drug is hypotonic, it may be necessary to add a substance to attain the proper tonicity range. Sodium chloride, boric acid, and dextrose are commonly used for this purpose. A tonicity of 300 mOsm/L is ideal, although a range of 200 to 600 mOsm/L is acceptable.

Sterility

Nasal preparations should be sterile. Sterility is best achieved through sterile filtration, which involves using a sterile membrane filter of 0.45 μ or 0.2 μ pore size and filtering into a sterile container. Other methods of sterilizing ingredients include dry heat, steam under pressure (autoclaving), and gas sterilization with ethylene oxide.

Other Excipients

Since most nasal preparations are prepared in multi-use containers, they must be preserved. The preservative used must be compatible with the active drug as well as with all other excipients in the product. Common preservatives that can be used for nasal products are shown in Table 20-1.

Antioxidants

Antioxidants may be required for selected active drug ingredients. Table 20-2 contains antioxidants that can be used in nasal preparations.

Quality Control

The compounding pharmacist should follow standard quality control procedures. These include checks for sterility, clarity (solutions), pH, and volume/weight. Sterility can be checked by plating a sample of the product on an agar plate and checking for microbial growth. If this procedure is not feasible, product samples can be sent to a laboratory for testing.

Packaging/Storage/Labeling

Containers for dispersing nasal preparations include dropper bottles, spray bottles (see Figure 20-3), and syringes (for gels and ointments). Generally, these preparations should be stored at either room temperature or refrigerated. They should not be frozen. These preparations should be labeled "For the Nose" and "Discard after [appropriate date]."

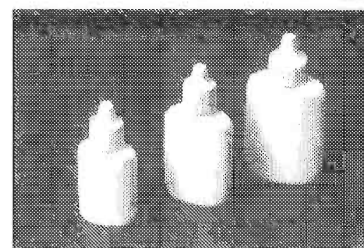


Figure 20-3. Nasal spray bottles in various sizes (15 mL, 20 mL, 30 mL).

Stability

Beyond-use dates for water-containing formulations are no later than 14 days, when stored at cold temperatures, for products prepared from ingredients in solid form. If nonaqueous liquids are prepared using a manufactured product, the beyond-use recommendation is no later than 25% of the time remaining on the product's expiration date or 6 months, whichever is earlier. For all other products, the beyond-use recommendation is the intended duration of therapy or 30 days, whichever is earlier. These beyond-use recommendations can be extended if valid scientific information is available to support the stability of the product, as discussed in Chapter 4, "Stability of Compounded Products."

Patient Counseling

When systemic therapeutic drugs, such as dihydroergotamine mesylate or morphine sulfate, are to be administered, the pharmacist should calibrate a dropper or spray container to deliver a consistent and uniform dose. The patient should be taught how to use the dosage device properly.

Sample Vehicle

R_x General Nasal Solution Vehicle

(pH 6.5 and isotonic)	
Sodium acid phosphate, hydrous	0.65 g
Disodium phosphate, hydrous	0.54 g
Sodium chloride	0.45 g
Benzalkonium chloride	0.05–0.01 g
Distilled water	qs ad 100 mL

1. Calculate the quantity of each ingredient required for the vehicle.
2. Accurately weigh or measure each ingredient.
3. Dissolve the ingredients in about 75 mL of the distilled water.
4. Adjust the pH to 6.5 if necessary.
5. Add sufficient distilled water to make 100 mL.
6. Filter through a 0.2 μ filter.
7. Package and label.

Sample Formulations

R_x Atropine Sulfate 0.5% Nasal Solution

Atropine sulfate	500 mg
Sodium chloride	835 mg
Sterile water for injection	qs 100 mL

1. Calculate the quantity of each ingredient required for the prescription.
2. Accurately weigh or measure each ingredient.
3. Dissolve the atropine sulfate and the sodium chloride in about 95 mL of sterile water for injection.
4. Add sufficient water for injection to make 100 mL.
5. Filter through a 0.2 μ filter into a sterile container.
6. Package and label.

R_x Desmopressin Acetate Nasal Solution 0.033 mg/mL

Desmopressin solution 0.1 mg/mL	2.5 mL
0.9% Sodium chloride solution	5 mL

1. Calculate the quantity of each ingredient required for the prescription.
2. Accurately weigh or measure each ingredient.
3. Mix the two solutions together and mix well.
4. Filter through a 0.2 μ filter into a sterile container.
5. Package and label.

R_x Saline Nasal Mist

Sodium chloride	650 mg
Monobasic potassium phosphate	40 mg
Dibasic potassium phosphate	90 mg
Benzalkonium chloride	10 mg
Sterile water for injection	qs 100 mL

1. Calculate the quantity of each ingredient required for the prescription.
2. Accurately weigh or measure each ingredient.
3. Dissolve the ingredients in sufficient sterile water for injection to make 100 mL of solution.
4. Filter through a 0.2 μ filter into a sterile solution.
5. Package in a nasal spray bottle.

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R_x **Xylometazoline Hydrochloride Nasal Drops**

Xylometazoline hydrochloride	100 mg
Sodium chloride	850 mg
Benzalkonium chloride	10 mg
Sterile water for injection	qs 100 mL

1. Calculate the quantity of each ingredient required for the prescription.
2. Accurately weigh or measure each ingredient.
3. Dissolve all the ingredients in sufficient sterile water for injection to make 100 mL.
4. Filter through a sterile 0.2 μ filter into a sterile container.
5. Package and label.

R_x **Progesterone 2 mg/0.1 mL Nasal Solution**

Progesterone	20 mg
Dimethyl- β -cyclodextrin	62 mg
Sterile water for injection	1 mL

1. Calculate the quantity of each ingredient required for the prescription.
2. Accurately weigh or measure each ingredient.
3. Dissolve the dimethyl- β -cyclodextrin in 0.9 mL of sterile water for injection.
4. Add the progesterone and stir until dissolved.
5. Adjust the pH to 7.4 using either dilute hydrochloric acid or dilute sodium hydroxide solution.
6. Add sufficient sterile water for injection to make 1 mL.
7. Package and label.

R_x **Scopolamine Hydrobromide 0.4 mg/0.1 mL Nasal Solution**

Scopolamine hydrobromide	400 mg
Buffer solution (pH 5)	5 mL
0.9% Sodium chloride solution	qs 100 mL

1. Calculate the quantity of each ingredient required for the prescription.
2. Accurately weigh or measure each ingredient.
3. Dissolve the scopolamine hydrobromide in about 50 mL of the 0.9% sodium chloride solution.
4. Add the pH 5 buffer and mix well.
5. Add sufficient 0.9% sodium chloride solution to volume and mix.
6. Filter through a 0.2 μ sterile filter into a sterile container.
7. Package in a metering nasal spray container and label.