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OPHTHALMIC DOSAGE FORMS

LEARNING OBJECTIVES

Upon completion of this lecture, you should be able to:

• Define buffers, buffer capacity, isotonicity, iso-osmoticity, osmotic pressure, hypertonicity, hypotonicity.

• Able to evaluate the appropriateness of the use buffers in pharmaceutical solutions.

• Able to evaluate the optimum pH range considered safe for a specific ophthalmic solution.

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OPHTHALMIC DOSAGE FORMS

LEARNING OBJECTIVES

- Demonstrate to prepare and analyze a buffer solution of desired pH and buffer capacity.
- Able to evaluate the importance of isotonicity in ophthalmic solutions.
- Demonstrate knowledge of the importance of sterility in ophthalmic solutions.
- Able to compare the appropriateness of different preservatives in pharmaceutical solutions.
- Able to demonstrate the calculations and preparations of pharmaceutically and physiologically acceptable ophthalmic solutions.

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OPHTHALMIC DOSAGE FORMS

Required Readings:

Preservatives:	Ansel 138-141
	Thompson Chapter 15
Antioxidants:	Thompson Chapter 16
Buffers:	Thompson Chapter 17
Viscosity enhancing Agents:	Thompson Chapter 18 (focus on ophthalmica)
Ophthalmica:	Ansel Chapter 17 Thompson Chapter 27

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Tears

normal tear volume=7 µl

volume that can be accommodated without spillage=30 µl

estimated drop volume =50 µl

blinking > residual volume of ~ 10 µl

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Tear film physiology

Tears are secreted by lacrimal glands at an average rate of about 1.5 mL/minute and empty at the surface of conjunctiva of the upper eyelid.

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Tear film physiology

When excess fluid is present in the eye, it drains down the nasolacrimal duct

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Tear film physiology

The functions of human tear film include:
(a) Removal of desquamated cells and debris from the eye,
(b) lubrication of cornea and lid interfaces,
(c) supply of oxygen to the corneal epithelium and stroma and
(d) prevention of drying-out of the anterior surfaces of the eye.

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Tear film physiology

The tear film is about 7 μm thick and is composed of three layers:
(a) lipid or oil layer,
(b) aqueous layer and
(c) mucin layer

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Tear film physiology

The exterior lipid layer is approximately 0.1-0.2 μm in thickness and consists of polar and nonpolar lipids.
Together, they establish and maintain a hydrophobic barrier that prevents tear overflow, retards evaporation and lubricates lid/ocular interface.
Removal of this layer increases the rate of evaporation of tears.

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Tear film physiology

Main components of the human tear film
Outer lipid layer
* Cholesterol esters
* Phospholipids
* Wax esters
* Free fatty acids
* Triglycerides
* Free sterols

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Tear film physiology

The middle aqueous layer constitutes the thickest portion of the tear film, and the lacrimal glands produce about 95 percent of it.
Continuous production and drainage of the aqueous tear layer are critical for a variety of functions, including cleaning the ocular surface by the flushing action of tear movement, regulation of osmotic flow and the supply of bacteriostatic agents for maintenance of antimicrobial activity.

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Tear film physiology

The aqueous layer contains electrolytes essential for corneal metabolism and regulation of osmotic flow of fluids between the corneal epithelial cells and the tear film.
Bicarbonate ions present in the aqueous layer regulate tear pH, whereas ions such as Mg+ and Ca++ act as enzyme co-factors.
Also present in the aqueous layer are the antimicrobial proteins, lysozyme and lactoferrin, that help protect the cornea from microbial invasion.

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Tear film physiology

Middle aqueous layer
* Water (98%)
* Glucose
* Lactate
* Citrate
* Glycoproteins
* Lysozyme
* Albumin
* Lactoferrin
* Mucopolysaccharides
* Na+, K+, Ca++, Mg++, Cl-, HCO3- and HPO42- ions
* Urea
* Amino acids

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Tear film physiology

The inner mucin layer coats the superficial epithelium of the cornea and conjunctiva and is produced predominantly by the goblet cells found throughout the conjunctiva, though lacrimal gland cells also produce tear mucins to some extent.

Mucins possess surface activity; in physiological concentrations, they lower the surface tension of pure water.

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Tear film physiology

Functionally, tear mucin facilitates corneal wetting, promotes adhesion between mucin and other layers of the tear film through hydrogen bonding and increases the stability of the tear film.

It is the presence of this mucin layer that converts the corneal epithelium from a hydrophobic to hydrophilic surface so that the tear film can be spread over the cornea

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Tear film physiology

- **Inner mucin layer**
- * Mucopolysaccahrides
- * Sialic acid
- * Glycoprotein

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OPHTHALMIC/OTIC DOSAGE FORMS

Ophthalmic products may be classified according to route of administration:

1.Topical

2.Intraocular

3.Systemic (oral and intra venous)

Most are administered by topical ophthalmic route. A number of issues are critical within these formulations, including **sterility**, **isotonicity** and the amount of **irritation** produced during administration

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Some pharmacological /therapeutic categories

Topical:

Anesthetics, anti-microbials, anti-inflammatory, astringents, beta adrenergic blocking agents, miotics, antihistamines, protectants, vasoconstrictors

Intraocular products:

to treat glaucoma (increased intraocular pressure)

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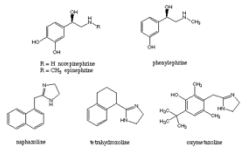
Some pharmacological /therapeutic categories



adrenergic
drugs cause vasoconstriction

phenylephrine naphazoline, tetrahydrozyline oxymetozoline

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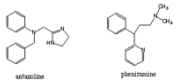
Some pharmacological /therapeutic categories

Ocular Antihistamines

antolazine
pheniramine



Ocular Antiseptics
boric acid

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Fluid removal by the naso-lacriminal apparatus

- take place when reflex tearing causes volume to exceed 7-10 µl
- eventually goes to GI tract: Potential systemic effects, salty/bitter taste
- superficial adsorption by drug through the conjunctiva: rapid removal by peripheral blood vessels

USP Ophthalmica

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Ointments see also USP <751><771>

Sterile, particle size, nonirritating, packaging

Solutions see also USP <789>

Sterile, particle free, buffered, isotonicity, preservatives, thickening agents, packaging

<789> Particle count: >10 um 50/mL >25 um 5/mL

Suspensions

Particle size

Strips

Fluorescein Sodium

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Ophthalmica

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 use ingredients that are nonirritating and compatible with the eyes during the formulation process.

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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

ADD FINAL PRODUCT TO STERILIZED CONTAINER

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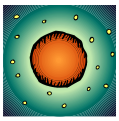
Solutions



Ophthalmic solutions are sterile, free from foreign particles and especially prepared for instillation into the eye.

General procedure:

- dissolve drug and all or part of excipients
- sterilize by heat of membrane filtration.
- if required, add the other sterilized excipients
- bring to volume with sterile solvent

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Eye drops

Solutions

- most ophthalmic drugs may be formulated as water-soluble salts
- the selection of the appropriate salt form depends on many properties

Example: epinephrine salts

Salts form	Discomfort reaction (stinging)	pH range	Buffer capacity
Hydrochloride	mild to moderate stinging	2.5-4.5	medium
Bitartarate	moderately to severe stinging	3-4	high
Borate	occasionally mild stinging	5.5-7.5	low

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Clarity

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.

Wetting/clarifying agents used for ophthalmic preparations

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

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Tonicity

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 2% 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 substance to attain the proper tonicity range.
- Sodium chloride, boric acid, mannitol, and dextrose are commonly used.

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Tonicity

- The eye generally tolerates hypertonic solutions more than hypotonic ones.
  e.g. sulfacetamide sodium solution
- Three hundred mOsm/L is ideal with 200-600 mOsm/L acceptable.

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Isotonicity Example

How much sodium chloride is required to render the following Rx isotonic?

Rx

Lidocaine HCl	1%	(NaCl equiv. = 0.22)
Cocaine HCl	1%	(NaCl equiv. = 0.16)
Epinephrine Bitartrate	0.1%	(NaCl equiv. = 0.18)
Sterile Water	qs50 mL	
Sodium Chloride	qs	

Calculations:
50 x .01 = 0.5 x .22 =0.110
50 x .01 = 0.5 x .16 =0.080
50 x .001 = .05 x .18 =0.009

0.199 g

The ingredients represent the equivalent of 0.199 g of NaCl.

50 x .009 = 0.45 g NaCl to make 50 mL water isotonic

0.45 - 0.199 = **0.251 g NaCl** needed to add to this Rx to make it isotonic

Buffers and Buffer Capacity

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- **Buffers** are compounds that resist changes in pH upon the addition of limited amounts of acids or bases. Buffer systems are usually composed of a weak acid or base and its conjugate salt.
- The components act in such a way that addition of an acid or base results in the formulation of a salt causing only a small change in pH.
- The pH of a buffer system is given by the Henderson-Hasselbach equation:
- $pH = pKa + \log \frac{[salt]}{[acid]}$ (for a weak acid and its salt)
- $pH = pKw - pKb + \log \frac{[base]}{[salt]}$ (for a weak base and its salt)
- where [salt], [acid] and [base] are the *molar* concentrations of salt, acid and base.

Buffers and Buffer Capacity

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- **Buffer capacity** is a measure of the efficiency of a buffer in resisting changes in pH.
- Conventionally, the buffer capacity (β) is expressed as the amount of strong acid or base, in gram-equivalents, that must be added to 1 liter of the solution to change its pH by one unit.
- Calculate the buffer capacity as: $\beta = \frac{\Delta B}{\Delta pH}$
- ΔB= gram equivalent of strong acid/base to change pH of 1 liter of buffer solution
- ΔpH = the pH change caused by the addition of strong acid/base
- In practice, smaller pH changes are measured and the buffer capacity is quantitatively expressed as the ratio of acid or base added to the change in pH produced (e.g., mEq./pH for x volume).

Buffers and Buffer Capacity

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- The buffer capacity depends essentially on 2 factors:
  - Ratio of the salt to the acid or base. The buffer capacity is optimal when the ratio is 1:1; that is, when pH = pKa
  - Total buffer concentration. For example, it will take more acid or base to deplete a 0.5 M buffer than a 0.05 M buffer.
- The relationship between buffer capacity and buffer concentrations is given by the Van Slyke equation:

$$\beta = 2.3\ C \frac{Ka[H_3O^+]}{(Ka + [H_3O^+])^2}$$

- where C = the total buffer concentration (i.e. the sum of the molar concentrations of acid and salt).

pH and Buffering

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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.

➢Target pH often the pH of maximum stability.

pH and Buffering

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pH and Buffering

➢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.

➢Must also consider pH-dependency of solubility

Sterility

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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)

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Sterility of eye drops

- the importance of sterility: since 1953, FDA has required sterile manufacture of all opthalmic solutions
- of great concern: Pseudomonas aeruginosa
- very common: Staphylococcus aureus,
- others: Candida albicans, Aspergillus niger, Escherichia coli
- a non-mandatory USP test is used by manufacturers to guide product development

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Preservative Challenge Test

Example: USP test for bacteria <51>, <341>

inoculated tubes are incubated at 20 or 25 °C for 28 days and examined at days 7,14,21, and 28.

By day 14, bacteria should be reduced to 0.1 % of the original count, and remain below for full 28 days.

manufacturers standard are usually more strict.

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Preservatives

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.

- preservatives not legally required in petroleum-based ointments

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Factors which may influence the effectiveness of preservatives:

- pH
- Solvent (emulsion, solution)
- Package material
- Nature of bioburden
- Nature of possible contamination
- Chemical stability
- Chemical properties e.g. surfactant
- Incompatibilities

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Mode of Action

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

- 1. Modification of cell membrane permeability and leakage of cell constituents (partial lysis)
- 2. Lysis and cytoplasmic leakage
- 3. Irreversible coagulation of cytoplasmic constituents (e.g., protein precipitation)

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Mode of Action

- 4. Inhibition of cellular metabolism, such as by interfering with enzyme systems or inhibition of cell wall synthesis
- 5. Oxidation of cellular constituents
- 6. Hydrolysis

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PROBABLE MODES OF ACTION

• Benzoic acid boric acid, p-hydroxybenzoates	Denaturation of proteins
• Phenols and chlorinated phenolic compounds	Lytic and denaturation action on cytoplasmic membranes and for chlorinated preservatives, also by oxidation of enzymes
• Alcohols	Lytic and denaturation action on membranes
• Quaternary compounds	Lytic action on membranes
• Mercurials	Denaturation of enzymes by combining with thiol (-SH) groups

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Anti microbial preservatives

1. Benzalkonium chloride (0.004-0.02%)

A quaternary ammonium compound

- Most widely used
- Very effective and fast acting
- Excellent chemical stability
- Some resistant strains of Pseudomonas aeruginosa
- Surfactant properties can affect corneal penetration
- Can adsorb to package components, large anions, surfactant, and others loss of potency

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Anti microbial preservatives

2. Thimerosal (0.001-0.02%) 0.01% typical for ophthalmic preparations

An organic mercurial

Precipitates in acid solutions

- Relatively weak and slow
- Hypersensitivity a problem.

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Anti microbial preservatives

3. Chlorobutanol (0.5%)

- Safe and effective but slow acting
- Most stable at below pH of 5
- Hydrolytic decomposition:
- over time reduces product pH
- Effective at concentrations as low as 0.125%
- Can permeate plastic containers.
- Avoid heat

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Anti microbial preservatives

4. Methyl- and propylparaben (Methyl- 0.03-0.1 % plus propyl 0.01-0.02%)

- Mostly used for molds
- Stinging and burning sensation
- Limited water solubility
- Bind to nonionic surfactants and polymers.

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Anti microbial preservatives

5. Polyquat (polyquaternium -1)

- Relatively new
- Does not penetrate the corneum well
- Almost nonsensitizing

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Preservatives

- When is it not necessary to add a preservative?
  - Immediate use
  - No water present
  - Ingredients are antimicorbial
  - pH of solution < 3 or 9>

Home work

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Preservative Name:	Usual Concentration:	Concentration Range:	Maximum Concentration:	Incompatibilities:
Chlorobutanol				
Quaternary Ammonium				soaps, anionic materials, salicylates, nitrates
Compounds:				
Benzalkonium chloride				
Benzethonium chloride				
Organic Mercurials:				Certain halides with phenylmercuric acetate.
Phenylmercuric acetate				
Phenylmercuric nitrate				
Thimerosal				
Parahydroxybenzoates				Adsorption by macromolecules.

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Antioxidants

Antioxidants may be required for selected active drug ingredients.

Antioxidant	Usual Concentration (%)
Ethylenediaminetetraacetic acid	0.10%
Sodium bisulfite	0.10%
Sodium metabisulfite	0.10%
Thiourea	0.10%

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Antioxidants

- Chelating agents
  - EDTA
- Oxygen scavengers (lower oxidation potential)
  - Sulfites, Ascorbic acid
- Chain terminators
  - Ascorbyl Palmitate
- Reducing agents
  - Ascorbic acid, Sodium Thiosulfate

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Viscosity enhancers

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.

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Viscosity enhancers

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

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Viscosity-increasing agents

- Increase retention time
- Reduce the drainage rate
- Increase ocular bioavailability

Examples: Cellulose derivatives (e.g. hydroxypropylmethyl- and methylcellulose) and polyvinyl alcohol.

- These agents also have a lubricant effect.
- Disadvantages: Crust formation and transient blurring

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Viscosity enhancers

Viscosity enhancers: 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.

Agent	Usual Concentration (%)
Hydroxyethylcellulose	0.8
Hydroxypropyl methylcellulose	1.00%
Methylcellulose	2.00%
Polyvinyl alcohol	1.40%
Polyvinylpyrrolidone	1.70%

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Miscellaneous agents

Surfactants -restricted use:

Used as wetting agents for suspensions, e.g., polysorbate-80

Toxicity: nonionic < cationic < anionic

May bind preservatives/ Use at the lowest level required

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Compounding TECHNIQUES aqueous 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.

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Example Vehicles

Isotonic Sodium Chloride Solution:

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

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Example Vehicles

Boric Acid Solution:

Boric Acid USP	1.9 g
Benzalkonium Chloride	1:10,000
Sterile Water for Injection	qs 100 mL

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Example Vehicles

Rx Artificial Tears:

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

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Oleanous Eye drops

Oils may be used for products too susceptible to moisture:

e.g., diisopropyl fluorophosphate in anhydrous peanut oil

But: oleanous preparations may blur vision

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Suspensions

Ophthalmic suspensions are sterile liquid preparations that contain solid particles in a suitable vehicle intended for instillation into the eye.

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.

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Suspensions

- For poorly soluble drugs or to improve stability and bioavailability.
- Mostly for topical steroidal anti-inflammatory agents.
- They do not provide a drug reservoir.
- particle size should be less than 10 µm

Example:

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The following procedure is given:

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.

Can you prepare the formulation according to this procedure?

Example:

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Answer

✓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.

What happens to the solubility of most drugs if the temperature increases?

✓7. If a large number are to be prepared, select a random sample to be checked for sterility and to be assayed.

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Example: What would be the correct method:

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 under aseptic conditions

4. Add **aseptically** 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.

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Powders for reconstitution

e.g. Phospholine Iodide (echothiopate iodide)

Advantage: longer shelf-life in the solid state.

Usually the drug is freeze-dried

Be careful when reconstituting!

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Semisolid dosage forms

•Most common: ointment

•Vehicle is usually mineral oil and white petrolatum

•Anhydrous and inert

•Most are suspensions

•Used frequently following surgery

•Are greasy and may blur vision

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Ointments

- sterilize the base by heat, then filter while molten to remove particulates
- place the molten base in a sterile mortar, or (heat-jacketed kettle).
- add sterilized drug and exipients aseptically
- mill the melt, if necessary, to disperse insoluble components

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Aqueous semisolid gel base

•A new formulation allow prolonged residence time in the cul-de-sac/ Increases bioavailibily.

•Utilizes carbomer, a high MW, cross-linked acrylic acid copolymer

•High viscosity optimal rheological properties fore ocular retention

•Low concentration of polymer, 95% water

e.g. Pilopine HS gel 24 hour duration of policarpine effect

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Packaging of ointments

•Usually packaged in small collapsible tubes holding 3.5 g

•Usually tin

•USP test to limit the level of metal particles <751>

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Packing of eye drops

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

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Packing of eye drops

Packaged almost entirely in plastic dropper bottles since the introduction of the Drop-Trainer bottle in the 50's.

- Made of low-density polyethylene (LDPE)
- Wide compatibility range
- Problems with sorption and permeability
- Can be made light-resistant with titanium dioxide
- Standard volumes: 5,15, and 30 ml.
- Tips and caps form a seal with tip when tightly screwed on.
- Glass dropper bottles are still used for some products: e.g., oxygen-sensitive drugs and freeze-dries products
- The sterile dropper (glass or LDPE with rubber bulb) is carefully tested for compatibility.

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Storage/Labeling

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

Label all ingredients and preservatives!

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Considerations in preparing ophthalmic solutions

Compliance

- clarity
- tonicity
- sensations
- viscosity enhancers
- proper packaging

Pharmaceutical Quality

- clarity
- tonicity
- pH/buffers
- sterility
- preservatives
- antioxidants
- viscosity enhancers
- proper packaging
- proper labelling
- proper expiration date

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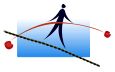
Stability



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 recommendations can be extended if there is supporting valid scientific stability information, as explained in the General Compounding Chapter of the United States Pharmacopeia

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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.

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Learning questions

- 1) When do you add preservatives to an ophthalmic solution?
- 2) How do you adjust the isotonicity of AgNO3 ophthalmic solutions?
- 3) Why can you taste eye drops after you administer them and which consequence has this for the drug used?
- 4) Why can you administer suspensions to the eye?
- 5) How do you calibrate a sprayer for a nasal preparation?

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Learning questions

- 6) What are important compliance aspects of eye drops?
- 7) What are the different mechanism of thiomersal and benzalkonium chloride to be used as a preservative?
- 8) When can you use EDTA used as antioxidants and in which cases is EDTA not suitable?
- 9) How can you measure the particle size in an ophthalmic ointment?
- 10) Which pharmaceutical quality characteristics are the same form ear, eyes and ophthalmic preparations?

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USP

- Otic solutions, intended for instillation in the outer ear, are aqueous, or they are solutions prepared with glycerin or other solvents and dispersing agents (e.g. Antipyrine and Benzocaine Otic Solution….)
- Otic Suspensions are liquid preparations containing micronized particles intended for instillation in the outer ear.

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Otic Solutions, Aural preparations

- Ph Eur Auricularia
  - Solutions, powders or semi solid
  - Drops, spray, rinse the ear
  - pH, tonicity, viscosity, preservatives
  - No irritation of the ear
  - Not to high pressure
  - For injuries or operations solution must be sterile, no preservatives, single dose
  - Normally preserved in multi dose unit

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Otic Solutions

- Ph Eur Auricularia
- Label all preservatives,
  - Auxiliary label: sterile, suspensions!
- Solutions with dropper, spray
  - Suspension particle size
  - Spray -> Praeparationes Pharmaceuticae in vasis cum pressu
- Ointments -> Unguenta

Otic preparations

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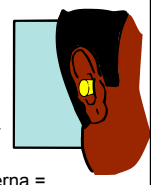
- Infections
- Pain
- Inflammation

Medications administered to the ear are only for local treatment



  - Mineral oils, detergents -> rinse with water
  - Neomycin, nystatin……aqueous,
  - propylene glycol, ->hygroscopic (otitis externa = swimmer's ear) Otic solution dries out he ear and controls indirect bacteria growth
  - inflammation,water for microorganisms
  - Cortisone -> pruritus (eyes and ear solutions)

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Ear products: solutions, suspensions and ointments

Cerumen removal

- •Cerumen (wax)
- •Formed by the secretion of sebaceous and apocrine glands, which include fats, proteins, carbohydrates, pigments and water
- •The secretion become a sticky semisolid that holds epithelial cells, fallen hair, dust, and other foreigh bodies
- •Old products contained light mineral oil, vegetable oils, and hydogen peroxide
  Newer products contain ceruminolityc agents;
- •Surfactant to emulsify: e.g., Cerumenex Drops
- •Triethanolamine polypeptide oleate-condensate in propylene glycol
- •Carbamide peroxide: e.g., Debrox: carbamide peroxide in glycerin/ propylene glycol

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Ear products: solutions, suspensions and ointments

Anti-infective: chloamphenicol, polymixin B sulfate, neomycin sulfate, acetic acid

Anti-inflammatory: hydrocortosine

Analgesic: benzocaine, antipyrine

Vehicles:

- •Often anhydrous, glycerin or propylene glycol
- •Viscous
- •Hygroscopic
- •Preservatives (e.g. chlorobutanol) and antioxidants (e.g. sodium bisulfite) are also used.
- •pH is important: Cortisporin Otic Suspension 4.8-5.1 over time pH = 3.0; Some generics 3.0-3.5; Pediotic 4.1

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Why Nasal?

- Nasal drug delivery offers multiple benefits such as fast onset, lower dose required, and ease of delivery.
- Intranasal delivery is more patient-friendly as it avoids the use of needles.
- This can improve compliance among patients who are afraid of needles and it decreases the risk of needle stick accidents.

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Nasal Delivery

- Nasal drug absorption is affected by molecular weight, size of the particles, pH and delivery volume.
- Generally, lower molecular weight drugs are more readily absorbed than higher molecular weight drugs.
- Particles should be larger than 10 microns to avoid lung deposition and the ideal particle size is between 10 and 50 microns.
- Particles larger than 50 microns may flow out of the nasal cavity, while particles between 10 and 20 microns also contain more medication.
- Nasal irritation is minimized if the drug pH falls within the range of 4.5 to 6.5.
- The delivery volume should be limited to the nasal cavity size.
- The 25 to 140 ul/nostril limit has been suggested to be the optimum delivery volume.

- *References:*
- */ McDonough Ph.D., Microcapsule Formulation, Controlled Release Microcapsule Formulation Design for Nasal Delivery.*
- *M Girous, P HwangM.D., A Prasad Ph.D., Nasal Drug Deposition, Controlled Particle Dispersion: Applying Vertical Flow to Optimize Nasal Drug Deposition.*

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Nasal Drug Successes

- Companies are starting to look at nasal drug delivery for a variety of drugs and vaccines. *Flonase* and *FluMist* are good examples of popular nasal drug delivery systems, which are paving the way for new nasal drugs.
- *Flonase,* developed by Glaxo-SmithKline for treatment of nasal symptoms of allergies, has been a blockbuster drug. *FluMist,* developed by MedImmune as a nasal flu vaccine, is the first nasal vaccine approved for use in the U.S.
- Vaccines are a growing area of interest for nasal drug delivery. One pharmaceutical company is developing an anthrax vaccine using nanotechnology-based alternative delivery systems, including nasal delivery systems.
- These successes are encouraging more companies to look at nasal drug delivery as a viable alternative to oral and injectable delivery methods.

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Nasalia

- Local
- Systemic
- No irritation of the mucous membrane
- No effect on ciliated epithelial cells (10 min)
- Aqueous isotonic, pH stability
- Preservatives (multi dose units)
- Glycerin and paraffin can dry out the mucous membrane (long time treatment)

- •For poorly absorbed drugs - alternative?
- •No first past effect

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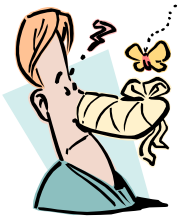
Nasal preparations (Nasalia)

- Liquids
- Semisolids
- Suspensions

Dosage forms
- Drops and spray
- Powder
- Ointments
- Rinsing solutions



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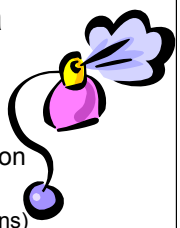
Nasalia



Drops or sprays
- Emulsion, suspension, solution
  - Aerosol
  - No phase separation (emulsions)
  - Easy to re suspend (suspension)
  - Dispenser for single dose
  - Particle size for nasal application

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Nasalia

- Decongestant adrenergic agents child and adult dose!
  - Oxymethazolem HCl 12 hours
  - Phenylepherine HCl 3 – 4 hours
- Rhinitis, hay fever
- Edema of mucous membrane
- Coadministration of NaCl can help to keep the mucous humid.

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Nasalia

- Peptide delivery
- For poorly absorbed drugs - alternative?
- No first past effect

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Nasal Solutions- Calibrating a Dropper/ Sprayer:

A nasally administered product has a dose of 25 µg. A 0.5% solution is prepared and placed in a nasal spray bottle. Ten "squeezes" into a plastic bag by the patient weighed 500 mg. How many squeezes are required to administer the 25 µg dose? (assume weight of solution is 1 gram per mL, *i.e.*, 500 mg = 0.5 mL). (0.5% = 0.5 g/100 mL)

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Attributes of a vehicle for nasal solutions

Compliance
- pH generally in the range of 5.5- 7.5
- Isotonic (200-600 mOsm/L)
- Does not modify mucus viscosity
- Dropper applicator

Pharmaceutical Quality
- pH generally in the range of 5.5- 7.5
- Mild buffer capacity
- Isotonic (200-600 mOsm/L)
- Does not modify mucus viscosity
- Compatible with the ciliary motion
- Compatible with ionic constituents of nasal secretions
- Compatible with active ingredient
- Stable
- Preserved multiple units/sterile in single units
- Dropper applicator

Compounding nasal preparations

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- **Preparation Methods/Techniques**
- **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 µ filter into a sterile nasal 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.

Compounding nasal preparations

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Is this the right method??

- **Preparation Methods/Techniques**
- **Suspensions:**
- 1. Accurately weigh/measure each of the ingredients.
- 2. Dissolve/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.

Compounding nasal preparations

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- **Preparation Methods/Techniques**
- **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 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.

Compounding nasal preparations

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- **Preparation Methods/Techniques**
- **Ointments:**
- 1. Accurately weigh/measure each of the ingredients.
- 2. Sterilize each of the ingredients by a suitable method.
- 3. Mix each of the ingredients with the sterile vehicle.
- 4. Determine the quality control factors from a sample of the product.
- 5. Package and label.
- 6. If a large number are to be prepared, select a random sample to be checked for sterility and to be assayed.

Compounding nasal preparations

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- **Preparation Methods/Techniques**
- **Gels:**
- 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. 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. Determine the pH, clarity and other quality control factors from a sample of the gel.
- 7. Package and label. (Sterile 1 mL syringes preloaded with individual doses work well).
- 8. If a large number are to be prepared, select a random sample to be checked for sterility and to be assayed.

Example

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- **RxGeneral Nasal Solution Vehicle (pH 6.5 and isotonic)**
- $NaH_2PO_4.H_2O$ 0.65
- $Na_2HPO_4.7H_2O$ 0.54
- NaCl 0.45
- Benzalkonium chloride 0.05-0.01%
- Distilled Water qs ad 100 mL