Pharmaceutical Solutions
Lecture 7 and 8

Ophthalmic solutions

By

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Ophthalmic Solutions

- Ophthalmic solutions are sterile solutions that are applied to the eye either for local effect or for treatment of interior parts of the eye
- These solutions should be isotonic, buffered to pH 7.4, viscous, and properly packaged
- Volume used, either small volume as eye drops or large volume
- Larger volumes of liquid preparations may be used cleaning solutions to flush or bathe the eye or for contact lenses.

Pharmacological categories of ophthalmic drugs

- The major categories of drugs applied topically to the eye are as follows:

1. **Anesthetics:** Topical anesthetics, such as tetracaine, cocaine, and proparacaine, are employed to provide pain relief preoperatively, postoperatively, for ophthalmic trauma, and during ophthalmic examination.
2. **Antibiotic and antimicrobial agents:** Used systemically and locally to combat ophthalmic infection.

- Among the agents used topically are azithromycin, gentamicin sulfate, sodium sulfacetamide, ciprofloxacin hydrochloride, ofloxacin, polymyxin B–bacitracin, and tobramycin.

1. **Antifungal agents:** Among the agents used topically against fungal endophthalmitis and fungal keratitis are amphotericin B, natamycin, and flucytosine.

4. **Anti-inflammatory agents:** Used to treat inflammation of the eye, as allergic conjunctivitis. Among the topical anti-inflammatory steroidal agents are fluorometholone, prednisolone, and dexamethasone salts. Nonsteroidal anti-inflammatory agents include diclofenac, flurbiprofen, ketorolac, and suprofen.
5. **Antiviral agents:** Used against viral infections, as that caused by herpes simplex virus. Among the antiviral agents used topically are trifluridine, ganciclovir, and vidarabine.
6. **Astringents**: Used in the treatment of conjunctivitis. Zinc sulfate is a commonly used astringent in ophthalmic solutions.

7. **Beta-adrenergic blocking agents:** Agents such as betaxolol hydrochloride, levobunolol metipranolol hydrochloride, and timolol maleate are used topically in the treatment of intraocular pressure and chronic open-angle glaucoma.
8. **Miotics and other glaucoma agents:** Miotics are used in the treatment of glaucoma, accommodative esotropia, and convergent strabismus and for local treatment of myasthenia gravis. Among the miotics are pilocarpine, echothiophate iodide, and demecarium bromide.
9. **Mydriatics and cycloplegics:** Mydriatics allow examination of the fundus by dilating the pupil. Mydriatics having a long duration of action are termed cycloplegics. Among the mydriatics and cycloplegics are atropine, scopolamine, homatropine, cyclopentolate, phenylephrine, hydroxyamphetamine, and tropicamide.

10. **Protectants and artificial tears:** Solutions employed as artificial tears or as contact lens fluids to lubricate the eye contain agents such as carboxymethyl cellulose, methylcellulose, hydroxypropyl methylcellulose, and polyvinyl alcohol.
11. **Vasoconstrictors and ocular decongestants:** Vasoconstrictors applied topically to the mucous membranes of the eye cause transient constriction of the conjunctival blood vessels. They are intended to soothe, refresh, and remove redness due to minor eye irritation.

- Among the vasoconstrictors used topically are naphazoline, oxymetazoline, and tetrahydrozoline hydrochlorides. Antihistamines, such as emedastine difumarate, ketotifen fumarate, and olopatadine hydrochloride, are included in some products to provide relief of itching due to pollen, ragweed, and animal dander.

Some instruction for uses of ophthalmic solutions

1. Because the capacity of the eye to retain liquid and semisolid preparations is limited (5-10 µl), topical application are administered in small amounts. Not more than one drop is put in the eye.
2. If we have multiple drop therapy, there should be at least 10 min between the applications of each type.

- Note that excessive liquids, both normally produced and externally delivered, rapidly drain from the eye.
- A single drop of an ophthalmic solution or suspension measures about 50 µL (based on 20 drops/mL), so much of an administered drop may be lost. The average dropper delivers about 25 to 50 µL/drop

2. Patient should not touch the tip of the dropper with the infected eye tissue.

Pharmaceutical requirements of ophthalmic solutions

1. Sterility and Preservation : all ophthalmic solutions or most should be sterilized using auto-clave at 121ºC for 15 min except those which are unstable at the auto-clave condition, they sterilized by another method such as by using micro-filter, which is a physical membrane that has pore size that prevent bacteria and foreign materials from passage into ophthalmic solution. However, this method is not efficient as auto-clave method. Other methods such as using of gases and rays can also be used.

- Ophthalmic solutions should be prepare in aseptic area, so all utensils and personnel should be clean and sterile, also the room are specially designing, so that the corner of the wall should be curvature and also there is a hood pushing sterile stream of air so push all bacteria and foreign bodies outside of the room.
- In addition to sterility, the ophthalmic solutions of multi-dose type should contain preservative, so that the microorganism introduced to solution accidently will show no growth.
- For ophthalmic solution used for surgical operation or for traumatized eye there is no need for preservative because:

1. some preservatives irritate the eye.
2. These preservative-free preparations are packaged in single-use containers.

The properties of the preservatives used in ophthalmic solutions

1. Should be effective at the used concentration.
2. Should be inert do not interact with active ingredient or container material.
3. Stable
4. Should not adsorb to the wall of the container.

Examples of preservative used in ophthalmic solutions

1. Benzylkonium chloride which is used in concentration between 0.004-0.01% w/v. It is quaternary ammonium compound, it acts as preservative by ion exchange with carboxyl group of cell wall of microorganism and it cause lyses of microorganism. It should not be used for anionic compound because it neutralized and its activity will impair.

2. Chlorbutanol is used in concentration 0.25-0.5% w/v. chlorobutanol cannot be autoclaved because it decomposes to hydrochloric acid even in moderate heat. This degradation renders a product susceptible to microbial growth and could alter its pH and thereby affect the stability and/or physiologic activity of the therapeutic ingredient. Efficient buffer should be used to prevent change in the pH of the product.

Isotonicity

- Ophthalmic solution should be isotonic with lachrymal fluid.
- Isotonic mean equal tone; if the ophthalmic solution is hypertonic so when applied to eye the solvent will get out of the cell, so we have shrinkage of eye tissue, and if the ophthalmic solution is hypotonic, so swelling occur to the tissue.
- In both cases discomfort feeling will result, for this reason tonicity should be adjusted. Eye can tolerate practically a tonicity 0.6-2% without marked discomfort to the eye. Sodium chloride itself does not have to be used to make the solution isotonic but boric acid in a concentration of 1.9% is used to produce the same osmotic pressure as does 0.9% sodium chloride.
- All of an ophthalmic solution's solutes, including the active and inactive ingredients, contribute to the osmotic pressure of a solution.

- Some of the drugs and the related values are presented in Table 17.2. The data are used in the following manner.
- Of each of the drugs listed, 1 g added to purified water will prepare the corresponding volume of an isotonic solution. For instance, 1 g of atropine sulfate will prepare 14.3 mL of isotonic solution. This solution may be diluted with an isotonic vehicle to maintain the isotonicity while changing the strength of the active constituent in the solution to any desired level.
- For instance, if a 1% isotonic solution of atropine sulfate is desired, 14.3 mL of isotonic solution containing 1 g of atropine sulfate should be diluted to 100 mL (1 g atropine sulfate in 100 mL = 1% w/v solution) with an isotonic vehicle.

Table 17.2 ISOTONIC SOLUTIONS PREPARED FROM COMMON OPHTHALMIC DRUGS

DRUG (1 G)	VOLUME OF ISOTONIC SOLUTION (ML)
Atropine sulfate	14.3
Boric acid	85.7
Chlorobutanol (hydrous)	26.7
Cocaine hydrochloride	17.7
Colistimethate sodium	16.7
Dibucaine hydrochloride	14.3
Ephedrine sulfate	25.7
Epinephrine bitartrate	20.0
Eucatropine hydrochloride	20.0
Fluorescein sodium	34.3
Homatropine hydrobromide	19.0
Neomycin sulfate	12.3
Penicillin G potassium	20.0
Phenylephrine hydrochloride	35.7
Physostigmine salicylate	17.7
Physostigmine sulfate	14.3
Pilocarpine hydrochloride	26.7
Pilocarpine nitrate	25.7
Polymyxin B sulfate	10.0
Procaine hydrochloride	23.3
Proparacaine hydrochloride	16.7
Scopolamine hydrobromide	13.3
Silver nitrate	36.7
Sodium bicarbonate	72.3
Sodium biphosphate	44.3
Sodium borate	46.7
Sodium phosphate (dibasic, heptahydrate)	32.3
Streptomycin sulfate	7.7
Sulfacetamide sodium	25.7
Sulfadiazine sodium	26.7
Tetracaine hydrochloride	20.0
Tetracycline hydrochloride	15.7
Zinc sulfate	16.7

- By using sterile drug, sterile purified water, a sterile isotonic vehicle, and aseptic techniques, a sterile product may be prepared. In addition to being sterile and isotonic, the diluting vehicles generally used are buffered and contain suitable preservative to maintain the stability and sterility of the product

Buffering

- Buffering of ophthalmic solutions means adjustment of ophthalmic solution pH close to lachrymal fluid pH 7.4 as much as possible.
- The benefits of buffering ophthalmic solutions are:

A. To reduce discomfort to the patient: the patient feels discomfort if ophthalmic solution pH is too high or too low, but after a short time he will fell comfort because the buffer capacity of tears get rid of excess H^+ ions or OH^- ions, but there are some drugs that are quite acidic that will overcome the buffer capacity of tears. Example of such drugs pilocarpine HCl and Epinephrine bitartarate.

B. To control stability: some drugs are unstable at the lachrymal fluid pH so another pH medium should be chosen.

C. To control therapeutic activity: if we want to treat the interior part of the eyes, then the drugs must be unionized to cross lipid membrane of the eye and this depend on pH. So we should select the pH that part of the drug will be ionized and part of it will be unionized; that a good thing for therapeutic activity and good for solubility.

D. To enhance the aqueous solubility of the drug. Solubility of alkaloidal salt is decreased at the pH level of lachrymal fluid pH and precipitates. So to adjust pH, a suitable pH buffer must be used.

USP described two buffers for ophthalmic solutions these are:

1. Boric acid buffer that provide pH slightly below 5, this buffer is suitable for many soluble salts of cocaine, phenylephrine, pilocarpine and tetracaine.
2. Phosphate buffer that provide a pH 5.9-8.0, it is suitable for many drugs except salt of pilocarpine, homatropine because they are unstable in this buffer.

- An isotonic phosphate vehicle prepared at the desired pH (Table 17.3) and adjusted for tonicity may be employed in the extemporaneous compounding of solutions.
- The desired solution is prepared with two stock solutions, one containing 8 g of monobasic sodium phosphate ($NaH_2 PO_4$) per liter and the other containing 9.47 g of dibasic sodium phosphate ($Na_2 HPO_4$) per liter, the weights being on an anhydrous basis

Table 17.3 ISOTONIC PHOSPHATE VEHICLE

MONOBASIC SODIUM PHOSPHATE SOLUTION (ML)	DIBASIC SODIUM PHOSPHATE SOLUTION (ML)	RESULTING BUFFER SOLUTION (PH)	SODIUM CHLORIDE REQUIRED FOR ISOTONICITY (G/100 ML)
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

- The vehicle is used effectively as the diluent for ophthalmic drugs already in isotonic solution, such as those prepared according to the method presented in Table 17.2.
- When drug substances are added directly to the isotonic phosphate vehicle, the solution becomes slightly hypertonic. Generally, this provides no discomfort to the patient. However, if such a solution is not desired, the appropriate adjustment can be made through calculated dilution of the vehicle with purified water

Viscosity and Thickening Agents

- In the preparation of ophthalmic solutions, a suitable grade of methylcellulose or other thickening agent is frequently added to increase the viscosity and thereby aid in maintaining the drug in contact with the tissues to enhance therapeutic effectiveness.
- Generally, methylcellulose of 4,000 cP is used in concentrations of 0.25% and the 25-cP type at 1% concentration.
- Hydroxypropyl methylcellulose and polyvinyl alcohol are also used as thickeners in ophthalmic solutions.
- Occasionally, a 1% solution of methylcellulose without medication is used as a tear replace.
- The optimal viscosity for ophthalmic solution is between 15 to 25 cps.

Additional Considerations

- Ophthalmic solutions must be sparkling clear and free of all particulate matter for comfort and safety. The formulation of an ophthalmic suspension may be undertaken when it is desired to prepare a product with extended corneal contact time, or it may be necessary when the medicinal agent is insoluble or unstable in an aqueous vehicle.
- Drug particles in an ophthalmic suspension must be finely subdivided, usually micronized, to minimize eye irritation and/ or scratching of the cornea. The suspended particles must not associate into larger particles upon storage and must be easily and uniformly redistributed by gentle shaking of the container prior to use.

Proper packaging

- The important thing is the product should be packed in a container so the solution is easily administrated, active constituents are stable and the sterility is maintained.
- We have two type of containers:

1. Glass containers
2. Plastic containers

- The disadvantage of glass containers is that the alkaline substance is leached from the glass container to ophthalmic solution causing an increase in the pH of the solution.
- The disadvantage of the plastic container is the interaction of the substance of the container with the preservative used or it allows separation of some medicinal agents.

- Although a few commercial ophthalmic solutions and suspensions are packaged in small glass bottles with separate glass or plastic droppers (screw dropper), most are packaged in soft plastic containers with a fixed built-in dropper.
- This type of packaging (fixed built-in dropper) is preferred both to facilitate administration and to protect the product from external.
- Ophthalmic solutions used as eyewashes are generally packaged with an eye cup, which should be cleaned and dried thoroughly before and after each use.

Contact lenses solutions

- Contact lenses may be hard, soft or rigid gas permeable (RGP).
- Solutions which are used for taking care of contact lenses are used as wetting solutions, cleaning solutions, soaking and storage solutions or combined purpose solutions (Combination solutions mix effects, such as cleaning and soaking, wetting and soaking, or cleaning, soaking, and wetting).
- It is very important to take care of contact lenses, if we do not take care of them then infection will takes place and if it occurs this may result in blindness, also if the lenses are not clean then it modify the sight.