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Review Article

REVIEW ON BASIC CONCEPT FOR OPTHALMIC PREPARATIONS

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ABSTRACT

Ocular drug delivery has been a major challenge to pharmacologists and drug delivery scientists due to its unique anatomy and physiology. Ophthalmic preparations are sterile liquid, semi-solid, or solid preparations intended for application to the conjunctiva, the conjunctival sac, or the eyelids. Sterility is very important factor in manufacture and use of ophthalmic products. Preservative selection is also an important activity in product design. Other important aspects requiring assessment in the manufacture of ophthalmic products include sterility, tonicity, pH, buffering, drug toxicity, solubility, stability, viscosity, aseptic filling, packaging and storage. Microbial content, in-process intermediates, and drug substance or active product ingredient are potential sources of contamination and require incoming testing of ingredients. The current developments in this field of ophthalmic drug delivery promise a significant improvement in overcoming the challenges posed by various anterior and posterior segment diseases.

INTRODUCTION [2]

Ophthalmic preparations (eye preparations) are sterile, liquid, semi-solid, or solid preparations that may contain one or more active pharmaceutical ingredient(s) intended for application to the conjunctiva, the conjunctival sac or the eyelids. The choice of base and any excipients used for the preparation of ophthalmic preparations must be proven through product development studies not to affect adversely either the stability of the final product or the availability of the active ingredients at the site of action. The addition of colouring agents is not recommended.

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The different categories of ophthalmic preparations include drops consisting of emulsions, solutions or suspensions, and ointments.

Manufacture

The manufacturing processes should meet the requirements of Good Manufacturing Practices, especially with regard to cross-contamination. The following information is intended to provide very broad guidelines concerning the main steps to be followed during production, indicating those that are the most important. Throughout manufacturing, certain procedures should be validated and monitored by carrying out appropriate in-process controls. These should be designed to guarantee the effectiveness of each stage of production. In-process controls during production of ophthalmic preparations should include monitoring environmental conditions (especially with respect to particulate and microbial contamination), pyrogens (use of a limulus amoebocyte lysate (LAL) test may be advantageous), pH and clarity of solution, and integrity of container (absence of leakage, etc.). Appropriate limits should be set for the particle size of the active ingredient(s). It is essential that ophthalmic preparations are

sterile. An aseptic manufacturing process is usually employed when the dosage form does not allow routine sterilization methods to be used.

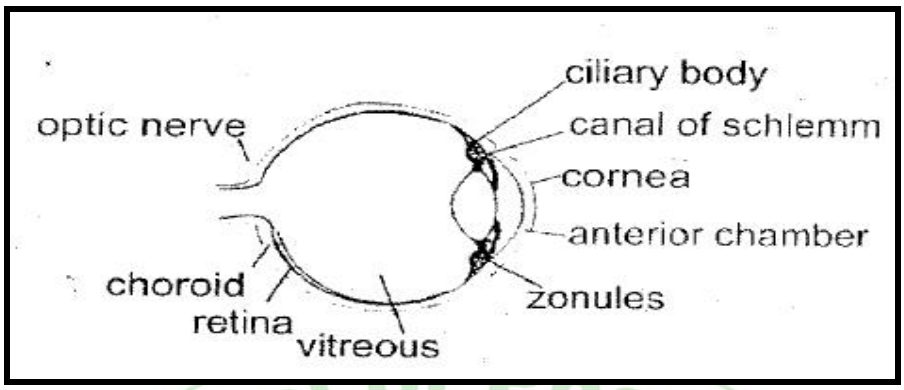

Figure 1: Schematic cross section through a human eye

Types of ophthalmic doses forms [2]

The different type of ophthalmic doses forms are-

- Opthalmic solutions
- Opthalmic suspensions
- Opthalmic ointments
- Opthalmic emulsions
- Opthalmic injections
- Ocular inserts and
- Contact lenses

Ophthalmic drops (solutions)

Ophthalmic drops (eye drops) are sterile aqueous or oily solutions, suspensions, or emulsions intended for instillation into the conjunctival sac. Ophthalmic drops should be clear and practically free from particles when examined under suitable conditions of visibility. "Water for injections" should be used in the manufacture of aqueous ophthalmic drops. The preparation of aqueous ophthalmic drops requires careful consideration of the need for isotonicity, a certain buffering capacity, the desired pH, the addition of antimicrobial agents and/or antioxidants, the use of viscosity-increasing agents, and the choice of appropriate packaging. Ophthalmic drops are considered isotonic when the tonicity is equal to that of a 0.9% solution of sodium chloride. The eye can usually tolerate solutions equivalent to 0.5–1.8% of sodium chloride. Ideally, the pH of ophthalmic drops should be equivalent to that of tear fluid, which is 7.4. However, the decision to add a buffering agent should be based on stability considerations. The pH selected should be the optimum for both stability of the active pharmaceutical ingredient and physiological tolerance. If a buffer system is used, it must not cause precipitation or deterioration of the active ingredient. The influence on the lachrymal flow should also be taken into account.

Example: Physostigmine eye drops.

Formula	Quantity
Physostigmine Sulphate	0.5 g
Sodium Metabisulphite	0.2 g
Benzalkonium Chloride	0.02 ml
Purified Water	Upto 100 ml

Visual inspection

Evidence of physical instability is demonstrated by the cloudiness of aqueous solutions, due to the formation of a precipitate.

Containers

Ophthalmic drops are normally supplied in suitable multidose containers that allow successive drops of the preparation to be administered. The container should be fitted with a tamper-evident device. The maximum volume of the preparation in such a container should be no more than 10 ml, unless otherwise specified and authorized. Multidose ophthalmic drop preparations may be used for up to 4 weeks after the container is initially opened. Droppers supplied separately should also comply with the "Test for sterility". Ophthalmic drops may also be provided in suitable single-dose containers that will maintain the sterility of the contents and the applicator up to the time of use. It is recommended that single-dose containers for surgical use should not include any antimicrobial agents.

Ophthalmic emulsions

These are sterile doses forms of poorly water soluble drugs dissolved in a non-aqueous vehicle and emulsified with water using a surfactant. They are administered in the form of drops into the conjuctival sac. They show better intra ocular penetration then suspension. Ophthalmic emulsions are generally dispersions of oily droplets in an aqueous phase. There should be no evidence of breaking or coalescence.

Example: Difluprednate eye emulsion

Formula	Quantity
Difluprednate	0.010 g
Castor oil	1 g
Polysorbate 80	0.8 g
Purified water	Upto 20 ml

Ophthalmic suspensions

Ophthalmic suspensions contain solid particles dispersed in a liquid vehicle; they must be homogeneous when shaken gently and remain sufficiently dispersed to enable the correct dose to be removed from the container. A sediment may occur, but this should disperse readily when the container is shaken, and the size of the dispersed particles should be controlled. The active ingredient and any other suspended material must be reduced to a particle size small enough to prevent irritation and damage to the cornea.

Visual inspection

Evidence of physical instability is demonstrated by the formation of agglomerates or precipitates in aqueous solutions (suspensions) that do not disperse when the solution is shaken gently.

Example: Fluorometholone eye suspension

Formula	Quantity
Fluorometholone	0.020g
Neomycine sulphate	0.100g
Polyvinyl alcohol	0.280g
Benzalkonium chloride	0.002g
Purified water	Upto 20ml

Ophthalmic ointments

Ophthalmic ointments are sterile, homogeneous, semi-solid preparations intended for application to the conjunctiva or the eyelids. They are usually prepared from non-aqueous bases, e.g. soft paraffin (Vaseline), liquid paraffin, and wool fat. They may contain suitable additives, such as antimicrobial agents, antioxidants, and stabilizing agents. The drug enters the eye through the cornea by simple diffusion they interfere with the vision and are suitable for use at bed time.

Organoleptic inspection

Evidence of physical instability is demonstrated by:

- A noticeable change in consistency, such as excessive "bleeding" (separation of excessive amounts of liquid) or formation of agglomerates or grittiness;
- Discoloration;
- Emulsion breakdown;
- Crystal growth;
- Shrinking due to evaporation of water; or
- Evidence of microbial growth.

Uniform consistency

Ophthalmic ointments should be of uniform consistency. When a sample is rubbed on the back of the hand, no solid components should be noticed.

Containers

Ophthalmic ointments are normally supplied in small, sterilized, collapsible tubes fitted with a tamper-evident applicator. The containers or the nozzles of the tubes are shaped so that the ointment can be applied without contaminating what remains in the tube. The content of such a container is limited to not more than 5g of the preparation. Suitable single-dose containers may also be used.

Example: Atropine sulphate eye ointment

Formula	Quantity
Atropine sulphate	0.1g
Wool fat	1g
Liquid paraffin	1g
Yellow soft paraffin	Upto 8g

Opthalmic injections

These are sterile solutions of drugs to be injected directly into the anterior chamber of the eye, drug like acetylcholine and steroids are administered as injections. These are directly injected into the eye, they should be pyrogen free and the particulate matter should be within the specified limits. They contain drug like anti-viral, miotics and visoelastics (used during surgery) this route is frequently used to administer drugs.

Ocular inserts

Ophthalmic inserts and ocular systems are solid dosage forms of appropriate size and shape that are placed in the conjunctival fornix, in the lachrimal punctum, or on the cornea. Inserts can usually be removed if adverse effects develop. They provide extended-release of the drug over a certain period of time. They can be classified as erodible (soluble) or nonerodible (insoluble). Drug release from soluble inserts involves two steps: (1) fast release of a portion of the drug as the tear fluid penetrates into the system, and (2) slow release as a gel layer is formed on the surface of the insert. Collagen shields made from porcine sclera collagen or bovine corium tissue, and devices obtained by molding, extrusion, or compression (mini tablets) of gelling polymers, belong to this category. Bioerodible polymers (e.g., cross linked gelatin derivatives and polyesters) can be used to prepare erodible inserts. These matrices act as reservoirs or interact with the drug molecules through labile bonds Soluble inserts can have the drug incorporated into an erodible matrix such as hydroxypropyl cellulose, hyaluronic acid, carbomer, or polyacrylic acid. They may be placed in the lower culde- sac and generally dissolve within 12–24 h. Erodible polymeric products undergo gradual dissolution while releasing the drug, and the patient does not have to remove it following use. Insoluble inserts can have a reservoir or matrix structure. Their mechanism of action is based on diffusion of a fluid into the device, dissolving the drug, and creating a saturated solution released to the medium by

diffusion out of the insert. The inserts need to be removed after a certain period of time.

Contact lenses

These preparations are utilized in the care of the contact lenses. All these solution posses the following characteristics-

- pH adjusted to that of lacrimal fluid.
- Non reactive with lens.
- Isotonic with the lachrymal fluid.
- Chemically stable
- Sterile in nature.

Types of contact lenses:

Hard contact lenses

- Made of rigid plastic resin polymethylmethacrylate
- Impermeable to oxygen and moisture

Soft contact lenses

- Made of hydrophilic trasparent plastic, hydroxyethylmethacrylate
- Contain 30 –80% water so are permeable to oxygen
- Have two types: daily wear and extended wear Rigid gas permeable (RGP)
- Take the advantages of both soft and hard lenses, they are hydrophobic and oxygen permeable.

Advantages of hard contact lenses and RGP lenses:

- Strength durability
- Resistant to absorption of medications and environmental contaminants
- Visual acuity

Disadvantages:

- Require adjustment period of the wearer
- More easily dislodged from the eye

General requirements [3]

Containers

The materials for containers and closures should not adversely affect the quality of the preparation or allow diffusion of any kind into or across the material of the container into the preparation. The container should be fitted with a closure that minimizes microbial contamination and a device that reveals whether the container has ever been opened.

Visual inspection

Inspect the ointments, aqueous or oily solution, suspensions, or emulsions. Evidence of physical and/or chemical instability is demonstrated by noticeable changes in colour and odour.

Sterility

Ophthalmic preparations should comply with the "Test for sterility".

Particle size

Ophthalmic preparations containing dispersed solid particles should comply with the following test- Take a quantity of the preparation (shake the container gently if necessary) corresponding to at least 10mg of solid active ingredient and place in a counting cell or spread in a thin layer on a slide. Firmly apply a cover-glass and scan the whole area of the sample under a microscope. For each 10mg of solid active substance not more than 20 particles should have a maximum dimension greater than 25mm and not more than two of these particles should have a maximum dimension greater than 50mm. None of the particles should have a maximum dimension greater than 90mm.

Labelling

Every pharmaceutical preparation must comply with the labelling requirements established by Good

Manufacturing Practices.

- The label on the immediate container should include:
- The name of the pharmaceutical product;
- The name(s) of the active ingredient(s); International Non-proprietary Names (INN) should be used wherever possible;
- The concentration(s) of the active ingredient(s) and the amount or the volume of preparation in the container;
- The batch (lot) number assigned by the manufacturer;
- The expiry date, the utilization period, and, when required, the date of manufacture;
- Any special storage conditions or handling precautions that may be necessary;

- If applicable, the period of use after opening the container;
- Directions for use, warnings and precautions that may be necessary;
- The name and address of the manufacturer or the person responsible for placing the product on the market;
- If applicable, the name(s) and concentration(s) of antimicrobial agent(s) and/or antioxidant(s) incorporated in the preparation; and
- The statement "This preparation is sterile".

For single-dose containers the following minimum information should appear on the container (provided that the label on the packaging bears the information stated above):

- The name(s) of the active ingredient(s); International Non-proprietary Names (INN) should be used wherever possible;
- The concentration(s) of the active ingredient(s) and the volume of the preparation in the container;
- The name of the manufacturer; and
- The type of preparation.

Multidose preparations

Unless the active ingredient itself has antimicrobial activity, ophthalmic preparations supplied as multidose preparations may include a suitable antimicrobial agent. The antimicrobial activity should remain effective throughout the entire period of use.

Storage

Ophthalmic preparations should maintain their integrity throughout their shelf-life when stored at the temperature indicated on the label. If not otherwise stated, the storage temperature should not exceed 25 °C. Special storage recommendations or limitations are indicated in individual monographs.

Formulation of Opthalmic preparation [4]

Tonicity and Tonicity-Adjusting Agents:

The tonicity of aopthalmic solution should be adjust correctly(exhert a osmotic pressure equal to that of tear fluids, generaly agreed to be equal to 0.9% NaCl) a range of 0.5-2.0% NaCl equvivalency does not cause a marked pain and range of about 0.2-0.7% sholud be acceptable for most persons. Common tonicity adjusting ingridient are:NaCl, Kcl, Buffer salt, dextrose, glycerine, propylene glycol and mannitol.

pH Adjustment and Buffers:

pH adjustment is very important as pH affects:

- To render the formulation more stable
- The comfort, safety and activity of the product.

Eye irritation → increase in tear fluid secretion → Rapid loss of medication

- To enhance aqueous solubility of the drug.
- To enhance the drug bioavailability
- To maximize preservative efficacy

Ideally every product buffered to a pH of 7.4(The normal physiological pH of tear fluid) If buffers are required, their capacity is controlled to be as low as possible.

- To enable the tears to bring the pH of the eye back to the physiological range
- To avoid effect of buffers on tonicity

Examples of buffer vehicles used:

-Boric acid vehicle: pH of slightly below 5

-Isotonic phosphate vehicle: pH ranges from 5.9 -8

Surfactants:

The order of surfactant toxicity is anionic>cationic>>non-ionic.

There are several non-ionic surfactant are used in low concentration to add in dispersing steroid in suspensions and to achieve or improve solution clarity.

Some of the surfactant which are principally used are sorbiton ether esters of oleic acid (polysorbate or tween 20 and 80)

Stabilizers & Antioxidants:

Stabilizers are the ingredients which are to preparation to decrease the rate of decomposition of active ingredient. Antioxidants are principle stabilizers added to some opthalmic preparation, primarily those containing epinephrine, and other oxidizable drugs.

Example: Sodium bisulphite or metabisulphite are used in concentration up to 0.3% in epinephrine hydrochloride and bitartrate solution.

Viscosity-Imparting Agents:
Polyvinyl alcohol, methyl cellulose, hydroxyl propyl methyl cellulose, hydroxylethylcellulose and carbomers are generally used in parentral preparation as viscosity imparting agent. They increase the ocular contact time thereby they decrease the drainage rate, increase the mucoadhessiveness and increase drug bioavilability.

Vehicles:
In opthalmic preparation generally purified water USP are used as a solvent which may be obtained by reverse osmosis, deionization and distillation process. Some of the mineral oil, vegetable oil such as sesame oil castor oil which have highest purity are used in extemporaneous compounding.

Preservative
Preservatives are included in multiple-dose eye solutions for maintaining the product sterility during use. Preservatives not included in unit-dose package. The use of preservatives is prohibited in ophthalmic products that are used at the of eye surgery because, if sufficient concentration of the preservative is contacted with the corneal endothelium, the cells can become damaged causing clouding of the cornea and possible loss of vision. The most common organism is Pseudomonas aeruginosa that grow in the cornea and cause loss of vision.

Packageing [4,5]

Opthalmic preparation are generally packed in glass and plastics container which are sterile in nature the plastic container are generally used due to their lower weight lower cost and give more convenience in transportation and handeling. It provides flexibility and inertness for eg drop trainer, plastic dispenser. The plastic bottle used in opthalmic preparation are made up of LDPE (low ethelene density polyethene)
Advantage of LDPE-Compatible with a very wide range of drugs and formulation components
Disadvantage-Sorption and permeability characteristics e.g. volatile preservatives such as chlorobutanol
Weight loss by water vapor transmission.

LDPE resin is translucent, if the drug is light sensitive, additional package protection is required (using opacifying agent such as titanium dioxide).

LDPE resin sterilized by gamma irradiation or ethylene oxide.

Evaluation of opthalmic preparation

Sterility: Ophthalmic dosage forms shall meet the requirements of If the specific ingredients used in the formulation do not lend themselves to routine sterilization techniques, ingredients that meet the sterility requirements described in, along with aseptic manufacture, may be used. The immediate container for ophthalmic preparations shall be sterile at the time of filling and closing. It is mandatory that the immediate containers for ophthalmic preparations be sealed and tamper-proof so that sterility is ensured at the time of first use.

Antimicrobial preservatives: Antimicrobial agents must be added to preparations that are packaged in containers that allow for the withdrawal or administration of multiple doses, unless one of the following conditions prevails: there are different directions in the individual monograph, the substance contains a radionuclide with a physical half-life of less than 24 h, the drug product without additional agents is sufficiently microbicidal to meet the requirements of Antimicrobial Effectiveness Testing. Substances must meet the requirements of Antimicrobial Agents—Content. Acceptance criteria for antimicrobial preservative content in multiple-unit products should be established.

Uniformity of dosage units: This test is applicable to dosage forms packaged in single-unit containers. It includes both the mass of the dosage form and the content of the drug substance (s) in the dosage form. The test can be performed by either content uniformity or weight variation

Uniformity in containers: Semisolid drug products may show physical separation during manufacturing processes and/or during the shelf life. To ensure the integrity of the drug product, it is essential to evaluate the

uniformity of the finished product at the time of batch release and throughout its assigned shelf life.

Leachables and extractables: The packaging system should not interact physically or chemically with the preparation in any manner to alter the strength, quality, or purity of the drug product. The packaging system should meet the requirements in Elastomeric Closures for Injection, Containers—Glass , Plastic Materials of Construction , and Plastic Packaging Systems for Pharmaceutical Use. Further information regarding packaging systems testing can be found in Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems and Assessment of Drug Product.

Container closure integrity: The packaging system should be closed or sealed in such a manner as to prevent contamination or loss of contents and should provide evidence of being tamper-proof. Validation of container integrity must demonstrate no penetration of microbial contamination or chemical or physical impurities.

Specific Tests [5]

Viscosity: An increase in viscosity increases the residence time in the eye. However, drug diffusion out of the formulation into the eye may be inhibited due to high product viscosity. Ophthalmic ointments are designed to be of very high viscosity to prolong the residence time in the eye. This is not a compendial test but is part of the manufacturer's specification of the drug product. See Viscosity—Capillary Viscometer Methods, Rotational Rheometer Methods, and Rolling Ball Viscometer Method.

Antioxidant content: If antioxidants are present in the drug product, tests of their content should be established unless oxidative degradation can be detected by another test method such as impurity testing. Acceptance criteria for antioxidant content should be established. They should be based on the levels of antioxidant necessary to maintain the product's stability at all stages throughout its proposed usage and shelf life.

Resuspendibility / redispersability: Consideration must be given to establishing good physical stability of a suspension. If the particles settle and eventually produce a cake at the bottom of the container, they must redisperse readily at the time of use to achieve dosage uniformity.

Particle size and particle size distribution: The potential for any changes in the particle size of ophthalmic suspensions and emulsions needs to be evaluated through stability testing. Drop size: For ophthalmic drug products dispensed as drops, drop sizes may typically range from 20 to 70 µL. However, the drop size for any individual product should be controlled and maintained throughout the product shelf life. Added substances: Suitable substances may be added to ophthalmic preparations to increase stability unless proscribed in the individual monograph, provided they are harmless in the amounts administered and do not interfere with therapeutic efficacy or with responses to the specified assays and tests. The use of ingredients solely to impart a color, odor, or flavor is prohibited.

CONCLUSION

All approaches presented in the present review lead us to conclude that all system present some interest in ocular drug delivery. They improve ocular drug bioavailibity by increasing ocular drug residence time, diminishes side effect due to systemic absorption and diminishing the necessary therapeutic amount of drug for therapeutic response in anterior chamber. However, all systems have disadvantages associated with them. Hence there is a need for polymer pattern in which drug could be trapped physically to prolong drug residence time from corneal surface and preserve visual activity. Such systems should probably be more hydrophilic than the materials.

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