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A Review on Quality Analysis and Evaluation of Ophthalmic Products

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***Abstract*:** Ophthalmic products are sterile preparations that encompass specialized dosage forms which can be administered onto the external surface of the eye. The slightest inflammation in the eyes can cause intense soreness and cause eye infections, swelling, allergies, challenge vision, and can cause permanent harm and cause lack of vision as well. Therefore, all ophthalmic preparations are required to stringently follow analytical testings and evaluations. Procedures and recognized standards for testing ophthalmic preparations are labeled into quality tests and overall performance checks to evaluate the integrity, drug release, and different attributes that relate to in vivo drug overall performance of the ophthalmic preparations. Quality control of ophthalmic preparations consists of conventional checks which include identification, potency, purity, sterility particulate matter, and dissolution testing, etc. Other critical components requiring assessment withinside the manufacture of ophthalmic products encompass tonicity, pH, buffering, drug toxicity, solubility, stability, viscosity, aseptic filling, packaging, and storage. In addition to the quality analysis and evaluation, the appropriate formulation and evaluation of the preservative are crucial for the continuing safety of the purchaser or patient.

Keywords – Ophthalmic Products, Quality Control, Evaluation

I. INTRODUCTION

The sense of seeing or sight is of exceptional significance to humans. Vision presents the early caution system for threats to our survival, however additionally enriches our life by describing features of the world in line with texture, color, context, and depth. At an easy level, the visual system includes the attention and an extended chain of neural connections that extend from the retinal receptors via the visual pathway to the primary visual cortex of the cerebrum. The eye offers the optics to provide an image of the external world upon the retina. It is customized to deliver the electromagnetic waves of light power to the retinal receptors. Our belief in brightness is derived from the amplitude of a light source, while our belief in color is derived from the wavelength of a light source.

The human eye is a delicate extension of the brain, encased and guarded with the aid of the bones of the skull. The eye has 3 coats. The cornea forms the clear and transparent front part of the outer layer, via which light passes. The remaining outer layer of the eye is shaped by the tough, white sclera that protects the sensitive receptors within. The 2nd or center layer is referred to as the choroid and includes the blood vessels that deliver the attention with nutrients. The innermost layer includes the specialized receptor cells of the retina.

The human eye is an excellent organ and the capacity to see is certainly considered one of our highly precious possessions. Thus, the simplest requirements are essential for the compounding of ophthalmic preparations and therefore the finest care is required in their use. Ophthalmic arrangements are sterile liquid, semi-solid, or solid preparations which could incorporate one or greater active pharmaceutical ingredients. Ophthalmic preparations are meant for the conjunctiva, the conjunctival sac, or the eyelids. Although eye preparations incorporate a preservative, there's a prospect of microbial contamination after the package sterility seal has been impaired throughout the duration of use.

All ophthalmic preparations have to be sterile and basically free from foreign particles The preparation may also have numerous functions like healing, prophylactic, or palliative. The versatility of dosage form allows a therapeutic agent to be appropriate for the function of preparation. The therapeutically active formulation can be designed to offer a prolonged action for both convenience and reduction in dose frequency, improved bioavailability of an agent, or enhanced transport to the target tissue. The residence time of an ocular preparation can also additionally range from few seconds (ophthalmic solutions) to hours (gel, ointments), to months or years (intraocular or periocular dosage forms). Various ophthalmic formulations consist of an aqueous solution, aqueous suspension, ointments, and ocular inserts. Every ophthalmic product has to be sterile in its final container to prevent microbial infection of the eye.

The route of application for ophthalmic arrangements falls into 3 categories: topical, intraocular injections, and extra-ocular injections. Topical drug products are supposed to be administered to an ocular surface factor which includes the eyelid, conjunctiva, or cornea, and might produce local or systemic effects. Intraocular and extra-ocular injections are administered via external boundary tissue. The ophthalmic routes of administration include, but are not limited to, topical, sub-conjunctival, sub-tenons, sub-retinal, sub-choroidal, intra-corneal, intra-scleral, supra-choroidal, intra-vitreal, intracameral, justascleral, and retro-bulbar.

II. TYPES OF OPHTHALMIC PREPARATIONS

a) Eye Drops

Eye drops are supplied for use in: -

- Sterile single-dose plastic sachets.
- Multiple-dose amber fluted eye dropper bottles which encompass the rubber teat as part of the closed container or supplied separately.
- Plastic bottles with a vital dropper. A breakable seal suggests that the dropper or cap has no longer been removed in advance of initial use.

Because of the threat of microbial infection of eye dropper bottles during use, it's far essential to protect the product with a preservative. Eye drops for surgical theatre use must be supplied in single-dose containers. Examples of preservatives are phenylmercuric nitrate or acetate, chlorhexidine acetate, thiomersal, and benzalkonium chloride. As with all rubber components, the rubber teat must be pre-equilibrated with the preservative in advance of use. Thermo stable eye drops and lotions are sterilized at 121°C for 15 minutes. For heat-stable drugs, filtration sterilization observed through manner of approach of aseptic filling into sterile containers is necessary. Eye drops in plastic bottles are prepared aseptically.

b) Eye Lotions

Eye lotions are isotonic solutions used for laundry or bathing the eyes. They are sterilized through autoclaving in fairly large-amount containers (100 ml or greater) of colored fluted glass with a rubber closure and screw-cap or packed in plastic bins with a screw-cap or tear-off seal. They may moreover encompass a preservative if intended for intermittent domiciliary use for as much as 7 days. If intended for first aid or assessment purposes, however, no bactericide is included and any remaining solution is discarded after 24 hours.

c) Eye Ointments

Eye ointments are prepared in a semisolid base—e.g. Simple Eye Ointment BP, which incorporates yellow soft paraffin (eight parts), liquid paraffin (1 part), and wool fat (1 part). The base is filtered while molten to get rid of particles and sterilized at 160°C for 2 hours. The drug is integrated in advance than sterilization if heat-stable or added aseptically to the sterile base. Finally, the product is aseptically packed in sterile aluminum or plastic tubes. As the product consists of virtually no water, the threat of microorganisms proliferating withinside the ointment is negligible.

d) Emulsions

Topical ophthalmic emulsions are typically prepared with the aid of dissolving or dispersing the drug substance into an oil phase, including appropriate emulsifying and suspending agents and combining with water vigorously to form a uniform oil-in-water emulsion. Each phase is generally sterilized earlier than or in the course of charging into the mixing vessel. High-shear homogenization can be employed to lessen oil droplet size to a submicron size which may also enhance the physical balance of the oil micelles in order that they do not coalesce. The ensuing dosage form has to include small oil droplets; uniformly suspended Limited aqueous solubility of the drug substance is the maximum usual purpose to institute an ophthalmic emulsion.

The drug substance(s) may be added to the phase wherein it is soluble at the start of the manufacturing process, or it could be introduced after the emulsion is ready with the aid of an appropriate dispersion process. Emulsion physical stability may be measured with the aid of using light scattering techniques that signify oil-phase globule size distribution. Suitable surfactants can be added to enhance emulsion.

e) Strips

Ophthalmic strips may have one-of-a-kind ophthalmic uses, but now no longer restrained to, use as a diagnostic device to visualize defects or aberrations in the corneal epithelium or to measure the quantity of tear production. They are manufactured from filter paper and might include compounds consisting of fluorescein sodium. They are individually packed to maintain sterility till the instant of use.

f) Implants

Implants are injected or implanted into the intra-cameral or intra-vitreal cavities and they may be in distinctive shapes, such as a disc or skinny rod. They may be manufactured from non-biodegradable or biodegradable polymers. Biodegradable polymers may be used to form injectable solid implants. Among the forms of non-biodegradable solid implants are reservoir-kind implants anchored to the sclera, wherein the drug is released throughout a non-biodegradable semipermeable polymer. They may be manufactured from numerous substances inclusive of polyvinyl alcohol–ethylene vinyl acetate.

g) Contact Lens

Most contact lenses are worn for optical cause as a replacement to spectacles. Contact lenses are of 2 types: hard lenses, which might be hydrophobic, and soft lenses, which can be both hydrophilic and hydrophobic. The surfaces of lenses need to be wetted before use and wetting solutions are used for this purpose. Hard and more especially, soft lenses emerge as contaminated with protein material in the course of use and consequently need to be wiped clean before disinfection. Contact lenses are potential assets of eye infection and, consequently, microorganisms have to be eliminated earlier than the lens is once more inserted into the eye. Lenses need to additionally be clean and easily wettable by lachrymal secretions. Contact lens solutions are therefore sterile solutions of the diverse sorts defined below.

- **Wetting solutions**
- **Cleaning solutions**
- **Soaking solutions**

III. QUALITY TESTING OF OPHTHALMIC PREPARATIONS

Procedures and acceptance criteria for testing ophthalmic preparations are divided into categories: -

- Assessment of general quality attributes, for example, identification, potency, purity (and impurities), sterility, and particulate matter.
- Assessment of in vitro product overall performance, i.e., dissolution or drug release of the drug substance from the drug product. Quality assessments investigate the integrity of the dosage form, while the overall performance assessments investigate drug release and different attributes that relate to in vivo drug overall performance. Taken together, quality and overall performance assessments guarantee the identification, strength, quality, purity, and efficacy of the drug product.

IV. DRUG PRODUCT QUALITY TESTS - UNIVERSAL TESTS

Universal tests are the assessments that are implemented to all ophthalmic products irrespective of the dosage form. The numerous universal assessments are: -

a. **Description**: - A qualitative description of the drug product must be provided. The acceptance criteria should contain the final appropriate appearance, which includes clarity and color, of the dosage form and packaging. If colour changes in the course of

storage, a quantitative method can be suitable. This is not a compendial check but is a part of the manufacturer's specification of the drug product.

b. **Identification**: - Identification assessments ought to set up the identification of the drug or drugs present withinside the article and must discriminate among compounds of intently related structures which are in all likelihood to be present. Identity assessments need to be unique for the drug substance.

c. **Assay**: - A unique and stability-indicating test has to be used to decide the strength of the drug product. In instances in which the usage of a nonspecific assay test is justified, different assisting analytical methods must be used to acquire usual specificity. A unique technique need to be used while there's proof of excipient interference with the nonspecific assay test.

d. **Impurities**: -Process impurities, synthetic byproducts, and different inorganic and organic impurities can be present in the drug substance and excipients used in the manufacture of the drug product. These impurities are managed through the drug substance and excipient monographs. Organic impurities arising from the degradation of the drug substance in the drug product and those arising in the course of the manufacturing procedure of the drug product shall be monitored.

e. **pH**: - Normal tears have a pH of approximately 7.4. The eye can tolerate preparations over a range of pH values from approximately 3.0 to approximately 8.6, relying on the formulation buffer capacity. The pH value of the formulation ought to be the only one in which the drug product is the maximum stable. Formulations that focus on the extremes of the acceptable pH variety can have higher patient acceptability in the event that they have a low buffering capacity.

f. **Osmolarity**: - Ophthalmic products can be tolerated over a reasonably extensive variety of tonicity. Hypotonic solutions are well tolerated than hypertonic solutions. Precautions must be taken to make certain that the product keeps its osmolarity in the course of the shelf life. Any possible contributions or interferences from the packaging system have to be considered.

g. **Particulate and Foreign Matter**: - All ophthalmic preparations, such as solutions, suspensions, emulsions, and implants, meant for ophthalmic injection have to be inspected to the extent possible for the presence of observable foreign and particulate matter. Qualification of the inspection approach has to be achieved concerning particulates in the visible variety and of a kind that would emanate from the producing or filling process. The inspection for visible particulates might also additionally take place in the course of inspection for different crucial attributes inclusive of molding abnormalities or cracked or faulty containers or seals, or while characterizing the appearance of lyophilized products.

Ophthalmic preparations, such as solutions, suspensions, emulsions, and implants and their packaging have to be advanced and manufactured in a way designed to exclude foreign visible particulate matter and to reduce the content of foreign sub visible particulate matter, as suitable for the dosage form.

Containers for ophthalmic use should be evaluated for cleanliness and want to be confirmed to be free of hard particulate matter which includes metallic or glass. Mainly for ophthalmic solutions, 100% inspection of all final packages is required.

h. **Sterility**: - Ophthalmic dosage forms shall meet the necessities of sterility assessments. The instant container for ophthalmic preparations will be sterile at the time of filling and closing. The immediate packing material for ophthalmic preparations needs to be sealed and tamper-proof just so sterility is ensured at the time of first use.

i. **Antimicrobial Preservatives**: - Antimicrobial agents have to be added to preparations that are packaged in containers that permit for the withdrawal or administration of more than 1 dose. Acceptance standards for antimicrobial preservative content in more than one unit of products must be established.

j. **Uniformity of Dosage Forms**: -This test applies to dosage forms packaged in single-unit containers. It consists of each the mass of the dosage form and the content material of the drug substance(s) withinside the dosage shape. The test may be accomplished through both content uniformity and weight variation.

k. **Uniformity in Containers**: - Semisolid drug products might also additionally display physical separation at some stage in production procedures and/or for the duration of the shelf life. To make sure the integrity of the drug product, it is vital to assess the uniformity of the finished product at the time of batch release and at some point of its assigned shelf life.

l. **Leachables and Extractables**: -the packaging system ought to not engage physically or chemically with the preparation in any way to alter the strength, quality, or purity of the drug product.

m. **Container Closure Integrity**: - The packaging system must be closed or sealed in any such way as to prevent contamination or loss of contents and have to offer proof of being tamper-evidence. Validation of container integrity has to show no penetration of microbial infection or chemical or physical impurities.

n. **Bacterial Endotoxins**: - Endotoxins are toxins that can't diffuse via the bacterial cell wall and are retained in the bacteria. They are released only while the cells die and begin disintegrating. The check for bacterial endotoxins (BET) measures the concentration of bacterial endotoxins that may be present withinside the sample or on the article to which the test has been implemented the usage of a lysate derived from the hemolymph cells or amoebocytes of the horseshoe crab, Limulus

polyphemus. Other species of horseshoe crab specifically Tachypleus gigas, Tachypleus tridentatus, and Carcinoscropius rotundicauda additionally yield amoebocyte lysate having comparable activity According to BP, There are three strategies for this test: the gel- clot technique, that's primarily based on gel formation; the turbidimetric technique, primarily based on the improvement of turbidity after cleavage of an endogenous substrate; and the chromogenic technique, primarily based totally on the improvement of color after cleavage of a synthetic peptide-chromogen complex.

V. DRUG PRODUCT QUALITY TESTS - SPECIFIC TESTS

a. **Viscosity**: - An increase in viscosity will increase the residence time in the eye. However, drug diffusion out of the formulation into the eye can be inhibited because of excessive product viscosity. Ophthalmic ointments are designed to be of very excessive viscosity to extend the residence time in the eye.

b. **Antioxidant Content**: - If antioxidants are present in the drug product, assessments in their content material have to be set up until oxidative degradation may be detected through any other test approach including impurity testing. Acceptance criteria for antioxidant content must be established. They must be based on the ranges of antioxidants vital to preserving the product's stability at all ranges during its proposed utilization and shelf life.

c. **Resuspendibility**: - Consideration has to be given to setting up the true physical stability of a suspension. If the particles settle and ultimately produce a cake at the bottom of the container, they have to redisperse effectively on the time of use to attain dosage uniformity.

d. **Particle Size and Particle Size Distribution**: - The capacity for any changes in the particle size of ophthalmic suspensions and emulsions needs to be evaluated via stability testing.

e. **Drop Size**: - For ophthalmic drug products dispensed as drops, drop sizes may also commonly vary from 20 to 70µl. However, the drop size for any individual product needs to be managed and maintained all through the product's shelf life.

f. **Added Substances**: - Suitable substances can be introduced to ophthalmic preparations to increase stability until prescribed in the individual monograph, provided they may be harmless in the quantities administered and do not intrude with therapeutic efficacy or with responses to the required assays and assessments. The use of components only to impart color, odor, or flavor is prohibited.

VI. DISSOLUTION/DRUG RELEASE TESTS

These tests are carried out to examine the drug release from the product matrix. In the case of semi-solid dosage forms including ointments, gels, emulsions, etc. The drug release assessments may be achieved through the use of varieties of equipment consisting of vertical diffusion cell, immersion cell, and a flow-through cell alongside the USP Apparatus 4. Depending on the design and launch mechanism of the dosage form, the dissolution/drug release test may be developed. Novel dosage forms may also require the usage of non-compendial equipment and/or conditions. The dissolution/drug release test ought to be discriminative for the crucial quality attributes of the product and have to be well validated.

VII.EVALUATION OF OPHTHALMIC PRODUCTS

The evaluation of ophthalmic preparations is carried out by the subsequent tests: -

- Sterility test
- Clarity test
- Leakage test
- Presence of metal particles

a. Sterility Test

Sterility is described as the absence of viable microbial contamination. Sterility is a definite requisite of all ophthalmic formulations. Contaminated ophthalmic formulations may also bring about eye infections that would in the long run lead to blindness, especially if the Pseudomonas aeruginosa microbe is involved.

Therefore, ophthalmic formulations have to be prepared in a laminar flow hood with the use of aseptic techniques just similar to intravenous formulations. The sterile formulations have to be packaged in sterile containers. As stated by USP and BP the sterility test can be accomplished by the use of the method of membrane filtration or by direct inoculation of the culture media with the product to be tested.

- **Membrane Filtration**:- The method of membrane filtration is used whenever the nature of the product allows, that is, for filterable aqueous preparations, for alcoholic or oily preparations, and for preparations miscible with or soluble in aqueous or oily solvents furnished the solvents that do not have an antimicrobial impact in the test conditions. The technique defined under assumes that membranes approximately 50 mm in diameter can be used.

  If filters of a certain diameter are used the volumes of the dilutions and consequently the washings must be adjusted duly. The filtration apparatus and membrane are sterilized. The equipment is designed just so the solution to be examined can be brought and filtered under aseptic situations; it permits the aseptic removal of the membrane for transfer to the medium.

- **Direct Inoculation of The Culture Medium**: - In agreement with BP, transfer the amount of the preparation to be examined prescribed into the culture medium in order that the quantity of the product isn't always greater than 10 percent of the quantity of the medium until in any other case prescribed. If the product to be tested has antimicrobial activity, perform the test after neutralizing this with an appropriate neutralizing substance or via way of means of dilution in enough amount of culture medium.

  When it is essential to apply a big quantity of the product it could be most appropriate to use a concentrated culture medium organized in the sort of manner that it takes account of the following dilution. Where appropriate, the concentrated medium is often added to the product in its container.

b. Clarity Test

Ophthalmic preparations have to be free from foreign particles. This is carried out by visual inspection under right light or with the aid of using instruments which include light scattering or video image projection.

- **Visual inspection**: - the preparation is tested under proper light, baffled against reflection into the eyes, and viewed against a black and white background with content set in movement with a swirling action.
- **Instrumental method: -** this technique makes use of the precept of light scattering, light absorption, and electric resistance to gain particle count and size distribution-destruction of product units. An instrumental technique making use of video image projection detects moving particles without destruction of product units-used for inline detection.

c. Leakage Test

This check is carried out for an ophthalmic ointment to assess the intact nature of the ointment tube and its seal.10 sealed containers are chosen and their exterior surfaces are cleansed.

- They are horizontally located over absorbent blotting paper in an oven saved at 60 ±three for eight hours. The check passes if leakage isn't always found from any tube.
- If leakage is determined the test is repeated with extra 20 tubes. The test passes if not greater than 1 tube indicates leakage out of 30 tubes.

d. Presence of Metal Particles

This test is needed only for ophthalmic ointments. The presence of metal particles will irritate the corneal or conjunctiva surface of the eye.

- It is carried out with the use of 10 ointment tubes. The content from every tube is fully withdrawn onto a clean 60mm diameter petri dish having a flat bottom.
- The lid is closed and the product is heated at eighty-five degrees Celsius for two hours. Once the product is melted and dispensed uniformly, it is cooled to room temperature.
- Remove the lid after solidification. The bottom surface is then examined via an optical microscope at 30 times magnification.
- The viewing surface has been illuminated using an external light source located at 45º at the top. The bottom surface of the ointment is examined and the amount of particles 50mm or greater is counted using a calibrated eyepiece micrometer.
- The USP recommends that the number of such particles in 10 tubes must not exceed 50, with not greater than 8 particles in any individual tube.

VIII.CONCLUSION

Ophthalmic preparations are sterile products that are meant for application to an ocular structure, as well as any area adjacent to an ocular structure and its immediate encompassing spaces. The preparation might have many functions like therapeutic, prophylactic, or palliative.

The versatility of dosage form permits a therapeutic agent to be appropriate for the function of preparation numerous ophthalmic formulations include aqueous solution, aqueous suspension, ointments, and ocular inserts. Each ophthalmic product should be sterile in its final container to stop microbial contamination of the eye.

Ophthalmic solutions ought to be prepared and preserved consistent with whether or not they are to be utilized in surgical procedures, within the clinic or office, or by the patient at home. Necessary factors to be thought-about in formulating an ophthalmic solution include clarity, sterility, osmolarity, pH, buffering, and preservation, stability in an acceptable vehicle viscosity, and appropriate packaging and storage of finished product.

Evaluation is the test of finished parenteral products, that either these preparations are free from a micro-organism or not. Evaluation of ophthalmic products is finished by conducting sterility tests, clarity tests, leakage tests, and metal particles in ophthalmic products.

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