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A Comparative study of quality control tests for eye preparations as per IP, BP and USP

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Abstract:
Present study deals with a brief review of the quality control tests for the eye preparations as per the different pharmacopoeias. The quality control tests for eye preparations are different in the different pharmacopoeias like IP, BP, and USP. Eye preparations are sterile liquid, semi-solid or solid preparations intended for administration upon the eyeball and/or to the conjunctiva, or for insertion in the conjunctival sac.It is necessary to know the quality requirements of the different pharmacopoeias for the eye preparations as it is required and important to guarantee the quality product and their supply in different markets of the world.
The main aim of the study is to compare the quality control tests for eye preparations as per the IP, BP and USP. The formulations which are taken in to consideration are eye drops, eye ointments, powders for eye drops and eye lotions, semi-solid eye preparations, ophthalmic inserts and eye lotions (or) eye solutions. The types of tests/parameters, procedures and the pharmacopoeial limits/specifications for eye preparations were compared.The quality control tests for different eye preparations are more elaborately given in IP and BP in comparison to USP. The available tests and limits supplement each other and one pharmacopoeia gives more details on a specific test than the other. For eg: Powders for eye drops and eyelotions, semi-solid eye preparations, ophthalmic insertswere specifically given in BP.

Keywords: IP, BP, USP, EYE CREAMS, EYE OINTMENTS, EYE LOTIONS

INTRODUCTION:

In the pharmaceutical industry, the product must be ensured to prevent the deviations from the specifications laid down by the pharmacopoeias and also it is necessary to control the errors during the process itself by performing the in-process checks. Quality is defined as "The sustainability of either a drug product or drug substance for its intended use". This term includes attributes as identity, strength and purity. Quality Control is that part of the GMP which is concerned with the sampling, specifications, testing of products for defects and reporting to management who makes the decision to investigate or deny the release.Both the in-process and finished product quality control tests helps to ensure the quality of the product. The entire in-process and finished product quality control tests involves stringent quality control tests to make products totally meeting the specifications before they are released into the market. In-process tests may be performed during themanufacture of either the drug substance or drug product to minimize the defects at the manufacturing stage itself, rather than as part of the formal quality control tests which are conducted prior to release. In-process quality controls (IPQC) are checks that are carried out before the manufacturing process is completed. The function of in process quality controls involves monitoring and if necessary, adaptation of the manufacturing process in order to comply with the specifications. This may include control of equipment and environment too. In-

process materials should be tested for their physical parameters and its quality attributes which are later approved or rejected by the quality assurance department based on the results obtained during the manufacturing process. Rejected in-process materials should be identified and controlled under a quarantine system designed to prevent their use in manufacturing. Standard operating procedures should be established and followed that describe the in-process controls and tests. Certain tests conducted during the manufacturing process, where the acceptance criterion is identical to the release requirement, (e.g., pH of a solution) which may satisfy requirements when the test is included in the specification. In-process controls may be performed at regular intervals during a processor at the end of the process. The objectives of in-process control are both quality control and process control.The classic interpretation of the term in process control includes the recording of measured values by members of the in process control group.[1]

Results & Discussions:

Quality control tests for Eye preparations:

Eye preparations are sterile liquid, semi-solid or solid preparations intended for administration upon the eyeball and/or to the conjunctiva, or for insertion in the conjunctival sac.

Several categories of eye preparations may be distinguished as:

- Eye drops
- Eye ointments
- Powders for eye drops and eye lotions
- Semi-solid eye preparations
- Ophthalmic inserts
- Eye lotions (or) Eye solutions

The quality control tests carried out for various eye preparations;

Eye drops

1. Uniformity of Volume
2. Particle size
3. Sterility

Eye ointments

1. Test for metal particles
2. Uniformity of weight
3. Particle size
4. Sterility
5. Leakage test

Powders for eye drops and eye lotions

1. Uniformity of dosage units
2. Content uniformity
3. Uniformity of mass

Semisolid eye preparations

1. Particle size

Ophthalmic inserts

1. Uniformity of dosage units
2. Content uniformity

Eye solutions or eye lotions

1. Isotonicity value
2. Buffering
3. Sterility

EYE DROPS:

Eye drops are sterile, aqueous or oily solutions or suspensions of one or more medicaments intended for instillation into the conjunctival sac. They may contain suitable auxiliary substances such as buffers, stabilizing agents, solubilizing agents and agents to adjust the tonicity or viscosity of the preparation.

Test procedure for eye drops

Uniformity of Volume

This complies with the tests for contents of packaged dosage forms.

Particle size

This test is applicable only to eye drops that are suspensions. Introduce a suitable volume of eye drops into a counting cell or onto a microscope slide, as appropriate. Scan under a microscope an area corresponding to 10 µg of the solid phase. Scan atleast 50 representative fields.

Sterility

The test must be carried out under aseptic conditions designed to avoid accidental contamination of the product during testing. For achieving these conditions, a grade A laminar air flow cabinet or anisolator is recommended. The test environment has to be adapted to the way in which the tests are performed.

Test procedures

Either of the following methods, Method A- Membrane Filtration or Method B- Direct Inoculation, may be followed.

Method A: After transferring the contents of the container or containers to be tested to the membrane add an inoculum of a small number of viable micro-organisms (not more than 100 CFU) to the final portion of sterile diluent used to rinse the filter.

Method B: After transferring the contents of the container or containers to be tested to the culture medium add an inoculum of a small number of viable micro-organisms (not more than 100 CFU) to the medium.[2]

Observations and interpretation of results

At intervals during the incubation period and its conclusion, examine the media for macroscopic evidence of microbial growth. If the material being tested renders the medium turbid so that the presence or absence of microbial growth cannot be determined easily by visual examination, 14 days after the beginning of incubation, transfer portions(each not less than 1ml) of the medium and then incubate the original and transfer vessels for not less than 4 days. If there is no evidence of microbial growth is found, the preparation under examination complies with the test for sterility. If evidence of microbial growth is found, the preparation under examination does not comply with the test for sterility. Do not repeat the test unless it can be clearly shown that the test was invalid for causes unrelated to the preparation under examination. The test may be considered invalid only when one or more of the following conditions are fulfilled:

- Microbial growth is found in the negative controls
- Data on microbial monitoring of the sterility testing facility show a fault
- A review of the testing procedure used for the test in question reveals a fault.[3]

EYE OINTMENTS

Eye ointments are sterile, semi-solid preparations of homogenous appearance intended for application to the eye. They may contain one or more medicaments dissolved or dispersed in a suitable basis. Bases, which are usually non-aqueous, may contain suitable auxiliary substances such as stabilizing agents, antimicrobial preservatives and antioxidants. The base selected must be non-irritant to the conjunctiva, allow the drug to diffuse throughout the secretions of the eye and retain the activity of the medicaments for a reasonable period of time under the stated conditions of storage.

Test procedures for Eye ointments

Uniformity of weight: ontents of packaged dosage forms for ointments

Select a sample of 10 filled containers and remove any labelling that might be altered in

weight while removing the contents of the containers. Clean and dry the outer surfaces of the containers and weigh each container. Remove quantitatively the contents from each container. If necessary, cut open the container and wash each empty container with a suitable solvent, taking care to ensure that the closure and other parts of the container are retained.

Particle size

Gently spread a small quantity of the eye Ointment as a thin layer on a microscope slide. Scan under a microscope an area corresponding to 10 µg of the solid phase. Scan at least 50 representative fields. Not morethan 20 particles have a maximum dimension greater than 25 µm, not more than 10 particles have a maximum dimension greater than 50 µm and none has a maximum dimension greater than 100 µm.

Sterility

The test must be carried out under aseptic conditions designed to avoid accidental contamination of the product during testing. For achieving these conditions, a grade A laminar air flow cabinet or an isolator is recommended. The test environment has to be adapted to the way in which the tests are performed. Precautions taken for this purpose should not adversely affect any microorganisms, which are to be revealed in the tests. The working conditions in which the tests are carried out should be monitored regularly by appropriate sampling of the air and surfaces of the working area and by carrying out control tests.

Test procedures

Either of the following methods, Method A- Membrane Filtration or Method B- Direct Inoculation, may be followed.

Method A: After transferring the contents of the container or containers to be tested to the membrane add an inoculum of a small number of viable micro-organisms (not more than 100 CFU) to the final portion of sterile diluent used to rinse the filter.

Method B: After transferring the contents of the container or containers to be tested to the culture medium add an inoculum of a small number of viable micro-organisms (not more than 100 CFU) to the medium.

Leakage test

Select 10 tubes of ointments, with seals when specified. Thoroughly clean and dry the exterior surfaces of each tube with an absorbent cloth. Place the tubes in a horizontal position on a sheet of absorbent blotting paper in an oven maintained at a temperature of 60 ± 3^0 C for 8 hrs. No significant leakage occurs during or at completion of the test (disregardstraces of ointment presumed to originate externally from within the crimp of the tube or from the thread of the cap). [4]

POWDERS FOR EYE DROPS AND EYE LOTIONS

Powders for the preparation of eye drops and eye lotions are supplied in a dry, sterile form to be dissolved or suspended in an appropriate liquid vehicle at the time of administration. They may contain excipients to facilitate dissolution or dispersion, to prevent caking, to adjust the tonicity, to adjust or stabilize the pH or to stabilize the preparation.

Test procedures for powders for eye drops and eye lotions

Uniformity of dosage units

To ensure the consistency of dosage unit, each unit in a batch should have an active substance content within a narrow range around the label claim. Dosage units are defined as dosage forms containing a single dose or part of a dose of an

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active substance in each dosage unit. Unless otherwise stated, the uniformity of dosage unit specification is not intended to apply to suspensions, emulsions or gels in single dose containers intended for cutaneous administration.

Content uniformity

Select not less than 30units, and proceed as follows for the dosage form designated.

For solid dosage forms like powders assay 10 units individually using an appropriate analytical method. Calculate the acceptance value (AV) using equation 1;

$$|M-X| + ks \ldots\ldots\ldots\ldots \quad (1)$$

Where,

$\overline{X}$ = mean of individual contents(x_1, x2……..x_n) expressed as a percentage of the label claim.

M= reference value

k = acceptability constant

s = sample standard deviation

Uniformity of content: The test for uniformity of content of single dose preparation is based on the assay of the individual contents of active substance of a number of single dose units to determine whether the individual contents are within the limits set with reference to the average contents of the sample.

Using the suitable analytical method, determine the individual contents of the active substances of 10 dosage units taken at random.The preparation complies with the test if each individual content is between 85% and 115% of the average content. The preparation fails to comply with the test if more than one individual content is outside the limits of 75% to 125% of the average content.If one individual content is outside the limits of 85% to 115% but within the limits of 75% to 125%, determine the individual contents of another 20 dosage units taken at random. The preparation complies with the test if not more than one of the individual contents of the 30units is outside 85% to 115% of the average content and none is outside the limits of 75% to 125% of the average content.

Uniformity of mass

Weigh individually 20 units taken at a random or, for single dose preparations presented in individual containers, the contents of 20units, and determine the average mass. Not more than 2 of the individual masses deviate from the average mass by more than the percentage deviation and none deviates by more than twice that percentage.Percentage deviation of powders for eye drops and eye lotions for average mass of less than 300 mg is 10

Percentage deviation of powders for eye drops or eye lotions foraverage mass of 300 mg or more is 7.5.[5]

SEMI-SOLID EYE PREPARATIONS

Semi-solid eye preparations are sterile ointments, creams or gels intended for application to the conjunctiva or to the eyelids. They contain one or more active substances dissolved or dispersed in a suitable basis. They have a homogeneous appearance.Semi-solid eye preparations comply with the requirements of the Semi-solid preparations for cutaneous application. The basis is non-irritant to the conjunctiva.Semi-solid eye preparations are packed in small, sterilized collapsible tubes fitted or provided with a sterilized cannula.

Test procedure for semisolid eye preparations

Particle size

Semi-solid eye preparations containing dispersed solid particles comply with the following test: spread gently a quantity of the preparation corresponding to at least 10 µg of solid active substance as a thin layer. Scan under a

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microscope the whole area of the sample. For practical reasons, it is recommended that the whole sample is first scanned at a small magnification (e.g. × 50) and particles greater than 25 µm are identified. These larger particles can then be measured at a larger magnification (e.g. × 200 to × 500). For each 10 µg of solid active substance, not more than 20 particles have a maximum dimension greater than 25 µm, and not more than 2 of these particles have a maximum dimension greater than 50 µm. None of the particles has a maximum dimension greater than 90 µm.

OPHTHALMIC INSERTS

Ophthalmic inserts are sterile, solid or semi-solid preparations of suitable size and shape, designed to be inserted in the conjunctival sac, to produce an ocular effect. They generally consist of a reservoir of active substance embedded in a matrix or bounded by a rate controlling membrane. The active substance, which is more or less soluble in lachrymal liquid, is released over a determined period of time. Ophthalmic inserts are individually distributed into sterile containers.

Test procedures for ophthalmic inserts

Uniformity of dosage units

To ensure the consistency of dosage unit, each unit in a batch should have active substance content within a narrow range around the label claim. Dosage units are defined as dosage forms containing a single dose or part of a dose of an active substance in each dosage unit. Unless otherwise stated, the uniformity of dosage unit specification is not intended to apply to suspensions, emulsions or gels in single dose containers intended for cutaneous administration.The term 'uniformity of dosage unit' is defined as the degree of uniformity in the amount of the active substance among dosage units.

The test of mass variation is applicable for the following dosage forms:

- Solutions enclosed in single dose containers and in soft capsules
- Solids (including powders, granules and sterile solids) that are packed in single-dose containers and contain no added active or inactive substances.

Content uniformity: Select not less than 30units, and proceed as follows for the dosage form designated.For solid dosage forms like powders assay 10 units individually using an appropriate analytical method. Calculate the acceptance value (AV) using equation 1;

$M-\bar{X}| + ks(1)$

Where,

$\bar{X}$ = mean of individual contents(x_1, x2……x_n) expressed as a percentage of the label claim.

M= reference value

k = acceptability constant

s = sample standard deviation

Single-dose powders for eye drops and eye lotions comply with the test or, where justified and authorized, with the tests for uniformity of content and/or uniformity of mass. Herbal drugs and herbal drugpreparations present in the dosage form are not subject to the provisions of this paragraph.

Uniformity of content

The test for uniformity of content of single dose preparation is based on the assay of the individual contents of active substance of a number of single dose units to determine whether the individual contents are within the limits set with reference to the average contents of the sample. Using the suitable analytical method, determine

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the individual contents of the active substances of 10 dosage units taken at random.

EYE SOLUTIONS OR EYE LOTIONS

Eye solutions or Eye lotions are sterile aqueous solutions intended for use in rinsing or bathing the eye or for impregnating eye dressings. Eye solutions or Eye lotions may contain excipients, for example to adjust the tonicity or the viscosity of the preparation or to adjust or stabilize the pH. These substances do not adversely affect the intended action or, at the concentrations used, cause undue local irritation.

Test procedures for eye solutions or lotions

Isotonicity value

Lachrymal fluid is isotonic with blood, having an isotonicity value corresponding to that of a 0.9% sodium chloride solution. Ideally an ophthalmic solution should have this isotonic value, but the eye can tolerate isotonicity values as low as that of a 0.6% sodium chloride solution and as high as that of a 2.0% sodium chloride solution without marked discomfort. Some ophthalmic solutions are necessarily hypertonic in orderto enhance absorption and provide a concentration of active ingredients strong enough to exert a prompt and effective action. Where the amount of such solutions used is small, dilution with lachrymal fluid takes place rapidly so that discomfort from the hyper tonicity is only temporary.

- Determine the number of moles of solute.
- Calculate the molarity of the solution
- Determine whether the solute dissociates as it dissolves.
- Determine which solutes can diffuse across the membrane and which cannot.
- Decide whether the solution is isotonic, hypertonic or hypotonic. An isotonic solution has the same tonicity on both sides of the membrane.

Buffering

One purpose of buffering some ophthalmic solutions is to prevent an increase in pH caused by the slow release of hydroxyl ions by glass. Such a rise in pH can affect both the solubility and the stability of the drug. Normal tears have a pH of about 7.4 and possess.some buffer capacity. The application of a solution to the eye stimulates the flow of tears and the rapid neutralization of any excess hydrogen or hydroxyl ions within the buffer capacity of the tears. Many ophthalmic drugs, such as alkaloidal salts, are weakly acidic and have only weak buffer capacity.

Sterilization: The sterility of a solutions applied to an injured eye is of great importance. Sterile preparations in special containers for individual use on one patient should be available in every hospital, office or other instillation where accidentally or surgically traumatized eyes are treated. The method of attaining sterility is primarily by the character of the particular product where ever possible, sterile membrane filtration under aseptic conditions is the preferred method. If it can be shown that product stability is not adversely affected, sterilization by autoclaving in the final container is also a preferred method.[6]

Table 1: Quality control tests for eye drops as per IP, BP and USP

Tests	IP	BP	USP
Uniformity of volume	✓	NS	NS
Particle size	✓	✓	NS
Sterility	✓	✓	NS

Table 2: Quality control tests for eye ointments as per IP, BP and USP

Tests	IP	BP	USP
Test for metal particles	✓	NS	✓
Uniformity of weight	✓	NS	NS
Particle size	✓	NS	NS
Sterility	✓	NS	✓
Leakage test	NS	NS	✓

Table 3: Quality control tests for Powders for eye drops and eye lotions as per IP, BP and USP

Tests	IP	BP	USP
Uniformity of dosage units	NS	✓	NS
Content uniformity	NS	✓	NS
Uniformity of mass	NS	✓	NS

Table 4: Quality control test for semisolid eye preparations as per IP, BP and USP

Tests	IP	BP	USP
Particle size	NS	✓	NS

Table 5: Quality control tests for ophthalmic inserts as per IP, BP and USP

Tests	IP	BP	USP
Uniformity of dosage units	NS	✓	NS
Content uniformity	NS	✓	NS

Conclusion

From the above review it is concluded that in IP, BP and USP most of the in-process and finished product quality control tests are included for eye preparations. However some differences were observed like some tests are mentioned in only one pharmacopoeia. The limits specified are also different for some tests mentioned in different pharmacopoeias. However the differences in these tests and limits / specifications mentioned needs to be harmonized and streamlined in such a way that if the test limits meets the harmonized limits then it must meet the requirements of all pharmacopoeias and the regulatory requirements of that particular countries. This is mainly important for the drugs which areglobally marketed. By this harmonization huge amount of man power, money and time can be minimized.[7]

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