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Quality Control Tests for Ophthalmic Pharmaceuticals: Pharmacopoeial Standards and Specifications

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Authors' contributions

This work was carried out in collaboration between all authors. Author MSU designed the study, wrote the protocol, managed the analyses of the study and prepared the draft of the manuscript. Authors AAM, MTK, JRS, SZ and YB managed the literature searches and participated in manuscript preparation. Author MSA reviewed the scientific contents of the manuscript. All the authors read and approved the final manuscript.

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ABSTRACT

The therapeutically performance of the pharmaceuticals must be constant and expectable. In order to claim a pharmaceutical to be a quality drug, it must fulfill certain standards and specifications. The quality of pharmaceuticals is strongly related to the patient's well-being. Quality control (QC) is an historical process in which proof is obtained that the appropriate level of quality has been achieved. QC can have no effect on the quality of the pharmaceuticals. It is merely a measuring process. QC must ensure that all the finished products contain active ingredients that comply with the qualitative and quantitative composition of the finished product described in the product

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registration dossier. The books containing the standards for drugs and other related substances are known as pharmacopeias. The pharmacopoeias contain a list of drugs and other related substances regarding their source, description, tests, formulas for preparing the same, action and uses, doses, storage conditions, etc. Ophthalmic pharmaceuticals are agents specially designed to be applied to the eyes. Among the drug products, ophthalmic pharmaceuticals are most important since eye is very sensitive and is easily irritated if the composition of the ophthalmic pharmaceutical is not suitable. The QC tests for ophthalmic pharmaceuticals are different in the different pharmacopoeias like IP, BP, and USP. Therefore the aim of this review was to mention QC tests for ophthalmic pharmaceuticals based on quality requirements of the different pharmacopoeias.

Keywords: Quality control; ophthalmic pharmaceuticals; pharmacopoeia; standard; specification.

1. INTRODUCTION

Ophthalmic pharmaceuticals are specialized dosage forms designed to be instilled onto the external surface of the eye (i.e., topical), administered inside (i.e., intraocular) or adjacent (i.e., periocular) to the eye or used in conjunction with an ophthalmic device [1,2]. The most commonly employed ophthalmic dosage forms are solutions, suspensions, and ointments [1,3]. Ophthalmic pharmaceuticals must be extraordinarily pure and free from physical, chemical, biological contaminants and suitably compounded and packaged for instillation into the eye [4]. These requirements imply a significant responsibility on the pharmaceutical industry to maintain current good manufacturing practices (cGMPs) in the manufacture of ophthalmic pharmaceuticals [5-7].

Quality is sustainability of drugs for their desired use measured by their efficiency, safety, consistent with label claim, or endorsed their conformity to specifications concerning identity, strength, purity and other characteristics [8]. According to International Organization for Standardization, quality control (QC) is the operational techniques and activities that are used to fulfill requirements for quality [9]. This statement could indicate that any activity whether serving the improvement, control, management or assurance of quality could be a part of the QC activity [10]. QC is the part of the GMP which is considered with the sampling, specifications, testing of products for defects and informing to management who makes the decision to examine or reject the release [11,12]. Both the in-process and finished product quality control tests aids to assure the quality of the product [13]. QC of pharmaceutical products is a concept that covers all measures taken, like the fixing of specifications, sampling, testing and analytical clearance, in order to assure that the raw materials, intermediates, packaging materials and finished pharmaceutical products comply with standard specifications for identity, strength, purity and other characteristics [14,15].

The development of a pharmaceutical is a long process concerning drug discovery, laboratory testing, animal studies, clinical trials and regulatory registration [16,17]. Furthermore, to improve the usefulness and safety of the drug product, various regulatory agencies, including European Medicines Agency, Food and Drug Administration, Medicines and Healthcare products Regulatory Agency and Therapeutic Good Administration are continuously developing rules and regulation in the Europe, US, UK and Australia respectively [18-20]. Pharmaceutical must be tested for its identity, strength, quality, purity and stability before the drug product can be released into the market [18-20]. Therefore, pharmaceutical validation and process controls such as raw materials inspection, in-process controls and targets for final product are very much crucial [21]. In fact the aim is to observe the on-line and off-line performance of the manufacturing process and then validate it. In addition, after the manufacturing process is validated, cGMP also needs so that a well-written procedure for process controls is established to monitor its performance [22,23].

The whole in-process and finished product QC tests contains rigorous testing of the quality parameters to make perfect finished pharmaceuticals [24]. In process quality control (IPQC) tests may be carried out before the manufacturing process is finished [6]. Generally, IPQC tests are performed at consistent intervals during a process towards the end of the process [25]. The function of IPQC requires monitoring and if needed, adaptation of the manufacturing process so as to meet with the specifications [26]. This may comprise both the control of equipment and environment [7,27]. The objectives of IPQC are both quality control and process control.

Finished pharmaceutical products are products which have passed all stages of production including packaging [28]. After completing the manufacturing process finished product quality control (FPQC) tests are performed with regard to qualitative and quantitative features accompanied by test procedures and their acceptance limits, with which the finished products must meet during the course of their effective shelf-life [29,30]. Different pharmacopoeias such as British Pharmacopoeia (BP), United States Pharmacopoeia (USP), European Pharmacopoeia (PhEur), International Pharmacopoeia (PhInt), Japanese Pharmacopoeia (JP) and Indian Pharmacopoeia (IP) give specific limits according to the regulatory requirements of that particular region [24].

The objective of this review was to suggest an outline of the quality parameters for pharmaceutical ophthalmic preparations in line with pharmacopoeial standards and specifications.

2. UNIVERSAL TESTS FOR OPHTHALMIC PHARMACEUTICALS

2.1 Description

This test is often called appearance on a specification and is a qualitative description of the ophthalmic pharmaceuticals. For example, the description of ophthalmic preparations on a specification may read: transparent/opaque preparation, proper labeling, imprinted with ‘‘Rx’’ [31].

2.2 Identification

The purpose of an identification or identity test is to verify the identity of the active pharmace utical ingredient (API) in the ophthalmic pharmaceuticals. This test should be able to discriminate between compounds of closely related structures that are likely to be present [32].

2.3 Assay

This test determines the strength or content of the API in the ophthalmic pharmaceuticals and is sometimes called a content test [33].

2.4 Impurities

This test determines the presence of any component that is not the API or an excipient of ophthalmic pharmaceuticals. The most common type of impurities that are measured is related substances, which are processed impurities from the new drug substance synthesis, degradation products of the API, or both [31].

3. QUALITY CONTROL PARAMETERS OF PHARMACEUTICAL OPHTHALMIC PREPARATIONS

QC testing of ophthalmic pharmaceuticals is an essential activity that helps to ensure their safety and efficacy. QC tests for ophthalmic pharmaceuticals based on pharmacopoeial standards and specifications are specified below:

3.1 pH

The pH of the ophthalmic pharmaceuticals is very important. Normal tears have a pH of about 7.4 and possess some buffer capacity. Many ophthalmic drugs, such as alkaloidal salts, are weakly acidic and have only weak buffer capacity. Where only 1 or 2 drops of a solution containing them are added to the eye, the buffering action of the tears is usually adequate to raise the pH and prevent marked discomfort [34]. In some cases pH may vary between 3.5 and 8.5. Some drugs, notably pilocarpine hydrochloride and epinephrine bitartrate, are more acid and overtax the buffer capacity of the lacrimal fluid. Ideally, an ophthalmic solution should have the same pH, as well as the same isotonicity value, as lacrimal fluid. This is not usually possible since, at pH 7.4, many drugs are not appreciably soluble in water [34]. Most alkaloidal salts precipitate as the free alkaloid at this pH. Additionally, many drugs are chemically unstable at pH levels approaching 7.4. This instability is more marked at the high temperatures employed in heat sterilization. For this reason, the buffer system should be selected that is nearest to the physiological pH of 7.4 and does not cause precipitation of the drug or its rapid deterioration [34].

The final pH of the solution is often a compromise, because many ophthalmic drugs have limited solubility and stability at the desired pH of 7.4 [35]. Buffers or pH adjusting agents or vehicles can be added to adjust and stabilize the pH at a desired level. Ophthalmic solutions are ordinarily buffered at the pH of maximum stability of the drug(s) they contain. The buffers are included to minimize any change in pH during the storage life of the drug; this can result from absorbed carbon dioxide from the air or from

hydroxyl ions from a glass container [35]. Changes in pH can affect the solubility and stability of drugs; consequently, it is important to minimize fluctuations in pH [35]. The buffer system should be designed sufficient to maintain the pH throughout the expected shelf-life of the product, but with a low buffer capacity so that when the ophthalmic solution is instilled into the eye, the buffer system of the tears will rapidly bring the pH of the solution back to that of the tears. Low concentrations of buffer salts are used to prepare buffers of low buffer capacity [35]. So the pH of the ophthalmic pharmaceuticals must be determined carefully by using suitable analytical method.

3.2 Isotonicity

The term isotonic, meaning equal tone [36]. A solution is said to be isotonic when its effective osmole concentration is the same as that of another solution. In biology, the solutions on either side of a cell membrane are isotonic if the concentration of solutes outside the cell is equal to the concentration of solutes inside the cell. In this case the cell neither swells nor shrinks because there is no concentration gradient to induce the diffusion of large amounts of water across the cell membrane [37].

Solutions that are isotonic with tears are preferred. An amount equivalent to 0.9% sodium chloride (NaCl) is ideal for comfort and should be used when possible. The eye can tolerate tonicities within the equivalent range of 0.6 to 2% NaCl without discomfort. There are times when hypertonic ophthalmic solutions are necessary therapeutically, or when the addition of an auxiliary agent required for reasons of stability supersedes the need for isotonicity. A hypotonic ophthalmic solution will require the addition of a substance (tonicity adjusting agent) to attain the proper tonicity range [35,38].

In circumstances when an ophthalmic solution without a buffer is desired, any compatible salt or non-electrolyte that is approved for ophthalmic products may be used. Sodium chloride, sodium nitrate, sodium sulfate, and dextrose are common neutral tonicity adjustors [35,38].

3.3 Viscosity

Viscosity measures the resistance of a solution to flow when a stress is applied. The viscosity of a solution is given in poise units [39]. The unit centipoise (cp or the plural cps) is equal to 0.01 poise and is most often used in pharmaceutical applications. Compounds used to enhance viscosity are available in various grades such as 15 cps, 100 cps, etc. The grade number refers to the viscosity that results when a fixed percentage aqueous solution is made. Generally the solutions are 1% or 2% and the viscosity is measured at 20°C [40].

Viscosity enhancers are used in ophthalmic solutions to increase their viscosity. This enables the formulation to remain in the eye longer and gives more time for the drug to exert its therapeutic activity or undergo absorption [40]. Commonly used viscosity enhancers and their maximum concentrations are given in the Table 1 [35,40].

Table 1. Typical concentrations of viscosity-enhancing agents approved for use in ophthalmic liquids [35,40]

Viscosity enhancer	Maximum concentration (%)
Hydroxyethylcellulose	0.8
Hydroxypropylmethylcellulose	1.0
Methylcellulose	2.0
Polyvinyl alcohol	1.4
Polyvinylpyrrolidone	1.7

The most common viscosity desired in an ophthalmic solution is between 25 and 50 cps. The actual concentration of the enhancer required to produce that viscosity will depend on the grade of the enhancer. For example, if methylcelluse 25 cps is used, a 1% solution will create a viscosity of 25 cps. If methylcellulose 4000 cps is used, a 0.25% solution provides the desired viscosity. Standard references give tables of viscosities produced by percentage solutions and grades of ingredients [35,40].

3.4 Therapeutic Efficacy

The active ingredient(s) should be present in the most therapeutically effective form. This goal must often be compromised for reasons of solubility or stability of the active ingredient or patient comfort. For example, while many drugs are most active in their undissociated form, they are least soluble in this form. They may also be less stable at pH values that favor the undissociated form [35,41].

3.5 Compatibility with the Eye

Ophthalmic solutions should be free of chemicals or agents that cause allergy or toxicity to the sensitive membranes and tissues of the eye. Auxiliary agents, such as preservatives and antioxidants, should be added with care because many patients are sensitive to these substances. Before adding an auxiliary agent, check with the patient about allergies and sensitivities [35,42].

3.6 Clarity

Ophthalmic solutions must be free from foreign particles, and this is generally accomplished by filtration. The filtration process also helps to achieve clarity of the solution. Table 2 contains a list of suitable clarifying agents. These agents are surfactants that improve aqueous drug solubility and are compatible with vehicles used to prepare ophthalmic liquids [35,43].

Table 2. Clarifying agents approved for use in ophthalmic preparations [35,43]

Clarifying agent	Usual concentration (%)
Polysorbate 20	1.0
Polysorbate 80	1.0

3.7 Particulate Matter

Particulate matter consists of particles that will not dissolve in solution other than gas bubbles that are unintentionally present on the product. Particulate matter can come from many sources in the processing. Limits for ophthalmic pharmaceuticals can be found in the pharmacopoeias [44].

According to USP this test is suitable for ophthalmic solutions. Particulate matter consists of mobile, randomly sourced, extraneous substances, other than gas bubbles, that cannot be quantitated by chemical analysis because of the small amount of material they represent and because of their heterogeneous composition [34].

Ophthalmic solutions should be essentially free from particles that can be observed on visual inspection. The tests described herein are physical tests performed for the purpose of enumerating extraneous particles within specific size ranges [34].

Every ophthalmic solution for which the monograph includes a test for Particulate matter is subject to the particulate matter limits set forth for the test being applied, unless otherwise specified in the individual monograph. When higher limits are appropriate, they will be specified in the individual monograph. Ophthalmic preparations that are suspensions, emulsions, or gels are exempt from these requirements, as are medical devices. Refer to the specific monograph when a question of test applicability occurs [34].

USP suggested light obscuration particle count (LOPC) and microscopic particle count (MPC) tests for the determination of particulate matter in ophthalmic solutions [34].

3.7.1 Light obscuration particle count test

This method analyzes the products using a light obscuration particulate analyzer [45]. According to USP, this test applies to ophthalmic solutions, including solutions constituted from sterile solids, for which a test for Particulate matter is specified in the individual monograph. The test counts suspended particles that are solid or liquid [34].

According to USP, the ophthalmic solution meets the requirements of the test if the average number of particles present in the units tested does not exceed the appropriate value listed in Table 3. If the average number of particles exceeds the limit, test the article by the Microscopic Particle Count Test [34].

Table 3. USP limits for particulate matters determined by LOPC test [34]

Nominal volume	Diameter	
	≥ 10 µm	≥ 25 µm
Number of particles	50 per mL	5 per mL

3.7.2 Microscopic particle count test

This method filters the products through a 0.8 µm grey gridded filter. The filter is then counted microscopically at 100× to determine the number of particles [46]. Some articles cannot be tested meaningfully by light obscuration. In such cases, individual monographs clearly specify that only a microscopic particle count is to be performed. The microscopic particle count test enumerates subvisible, essentially solid, particulate matter in ophthalmic solutions, after collection on a microporous membrane filter. Some ophthalmic solutions, such as solutions that do not filter readily because of their high viscosity, may be

exempted from analysis using the microscopic test [34].

When performing the microscopic test, do not attempt to size or enumerate amorphous, semiliquid, or otherwise morphologically indistinct materials that have the appearance of a stain or discoloration on the membrane surface. These materials show little or no surface relief and present a gelatinous or film-like appearance. Because in solution this material consists of units on the order of 1 µm or less, which may be counted only after aggregation or deformation on an analytical membrane, interpretation of enumeration may be aided by testing a sample of the solution by the light obscuration particle count method [34].

According to USP, the ophthalmic solution meets the requirements of the test if the average number of particles present in the units tested does not exceed the appropriate value listed in Table 4 [34].

Table 4. USP limits for particulate matters determined by MPC test [34]

Nominal volume	Diameter		
	≥ 10 µm	≥ 25 µm	≥ 50 µm
Number of particles	50 per mL	5 per mL	2 per mL

3.8 Insoluble Particulate Matter

This test is used to examine for the size and the number of insoluble particulate matter in aqueous ophthalmic solutions [47]. In line with JP, carry out preparations carefully in clean equipment and facilities which are low in dust. Fit the membrane filter onto the membrane filterholder, and fix them with the clip. Thoroughly rinse the holder inside the purified water for particulate matter test, and filter under reduced pressure with 200 mL of the purified water for particulate matter test at a rate of 20 to 30 mL per minute. Apply the vacuum until the surface of the membrane filter is free from water, and remove the membrane filter. Place the filter in a flat-bottom petri dish with the cover slightly ajar, and dry the filter fully at a temperature not exceeding 50°C. After the filter has been dried, place the petri dish on the stage of the microscope. Under a down-light from illuminating device, adjust the grid of the membrane filter to the coordinate axes of the microscope, adjust the microscope so as to get the best view of the insoluble particulate matter, then count the number of particles that are equal to or greater than 150 µm within the effective filtering area of the filter, moving the mobile stage, and ascertain that the number is not more than 1. In this case the particle is sized on the longest axis [48].

Fit another membrane filter to the filtration device, and fix them with the clip,then wet the inside of the filter holder with several mL of purified water for particulate matter test. Clean the outer surface of the container, and mix the sample solution gently by inverting the container several times. Remove the cap, clean the outer surface of the nozzle, and pour the sample solution into a measuring cylinder which has been rinsed well with purified water for perticulate matter test. Repeat the process to prepare 25 mL of the test solution. Pour the test solution into the filter holder along the inner wall of the holder. Apply the vacuum and filter mildly so as to keep the solution always on the filter. As for viscous sample solution, dilute suitably with purified water for particulate matter test or suitable diluent and then filter as described above. When the amount of the solution on the filter becomes small, add 30 mL of purified water for particulate matter test or suitable diluent in such manner as to wash the inner wall of the filter holder. Apply the vacuum gently until the surface of the membrane filter is free from water. Place the filter in a perti dish, and dry the filter at a temperature below 50°C with the cover slightly ajar. After the filter has been dried, place the petri dish on the stage of the microscope. And count the number of particles which are equal to or larger than 300 µm with in the effective filtering area of the filter according to the same procedure of the microscope as described above. In this case the particle is sized on the longest axis [48].

3.9 Particle Size

According to BP this test is suitable for eye drops. Unless otherwise justified and authorised, eye drops in the form of a suspension comply with the following test: introduce a suitable quantity of the suspension into a counting cell or with a micropipette onto a slide, as appropriate, and scan under a microscope an area corresponding to 10 µg of the solid phase. For practical reasons, it is recommended that the whole sample is first scanned at low 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 [49].

As said by IP, introduce a suitable volume of the 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 at least 50 representative fields. Not more than 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 [50].

Consistent with BP this test is also fit for semi-solid eye preparations. 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 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 [49].

This test is suitable for eye ointment. According to IP, 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 more that 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 [50].

3.10 Uniformity of Volume

Consistent with IP this test is appropriate for eye drops. For this test pour completely the contents of ophthalmic preparation of each container into calibrated volume measures of the appropriate size and determine the volume of contents of 10 containers [50].

According to IP the average net volume of the contents of the 10 containers is not less than the labeled amount, and the net volume of the contents of any single container is not less than 91% and not more than 109% of the labeled amount where the labeled amount is 50 ml or less; or not less than 95.5% and not more than 104.5% of the labeled amount where the labeled amount is more than 50 ml but not more than 200 ml; or not less than 97% and not more than 103% of the labeled amount where the labeled amount is more than 200 ml but not more than 300 ml [34]. Consistent with IP, if these requirements are not met, determine the net volume of the contents of 10 additional containers. The average net volume of the contents of the 20 containers is not less than the labeled amount, and the net volume of the contents of not more than 1 of the 20 containers is less than 91% or more than 109% of the labeled amount where the labeled amount is 50 ml or less or not less than 95.5% and not more than 104.5% of the labeled amount where the labeled amount is more than 50 ml but not more than 200 ml, or not less than 97% and not more than 103% of the labeled amount where the labeled amounts is more than 200 mL but more than 300 mL (Table 5) [50].

Table 5. IP limits for uniformity of volume [50]

Volume	Percentage deviation
≤ 50 mL	± 9%
50-200 mL	± 4.5%
200-300 mL	± 3%

3.11 Uniformity of Content

As stated by BP this test is appropriate for powders for eye drops and eye lotions. Unless otherwise prescribed or justified and authorised, single-dose powders for eye drops and eye lotions with a content of active substance less then 2 mg or less than 2 percent of the total mass comply with test. If the preparation has more than one active substance, the requirement applies only to those substances that correspond to the above condition [49].

According to BP, using a suitable analytical method, determine the individual contents of active substance(s) of 10 dosage units taken at random. The preparation complies with the test if not more than one individual content is outside the limits of 85 percent to 115 percent of the average content and none is outside the limits of 75 percent to 125 percent of the average

content. The preparation fails to comply with the test if more than 3 individual contents are outside the limits of 85 percent to 115 percent of the average content or if one or more individual contents are outside the limits of 75 percent to 125 percent of the average content [49].

On the word of BP, if 2 or 3 individual contents are outside the limits of 85 percent to 115 percent but within the limits of 75 percent to 125 per cent, determine the individual contents of another 20 dosage units taken at random. The preparation complies with the test if not more than 3 individual contents of the 30 units are outside the limits of 85 per cent to 115 percent of the average content and none is outside the limits of 75 per cent to 125 percent of the average content [49].

In line with BP this test is also fit for ophthalmic inserts. The test for uniformity of content of single-dose preparations is based on the assay of the individual contents of active substance(s) of a number of single-dose units to determine whether the individual contents are within limits set with reference to the average content of the sample [49]. The test is not required for multivitamin and trace-element preparations and in other justified and authorized circumstances.

According to BP, using a suitable analytical method, determine the individual contents of active substance(s) of 10 dosage units taken at random [33]. As said by BP, the preparation complies with the test if each individual content is between 85 percent and 115 percent of the average content. The preparation fails to comply with the test if more than one individual content is outside these limits or if one individual content is outside the limits of 75 percent to 125 percent of the average content [49].

Consistent with BP, if one individual content is outside the limits of 85 percent to 115 percent but within the limits of 75 percent to 125 per cent, 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 30 units is outside 85 percent to 115 per cent of the average content and none is outside the limits of 75 percent to 125 per cent of the average content [49].

3.12 Uniformity of Mass

In relation to BP single-dose powders for eye drops and eye lotions comply with the test. If the test for uniformity of content is prescribed for all the active substances, the test for uniformity of mass is not required [49].

Consistent with BP, weigh individually 20 units taken at random or, for single-dose preparations presented in individual containers, the contents of 20 units, and determine the average mass. Not more than 2 of the individual masses deviate from the average mass by more than the percentage deviation shown in Table 6 and none deviates by more than twice that percentage [49].

Table 6. BP limits for uniformity of mass [49]

Dosage form	Average mass	Percentage deviation
Powder for eye drops and eye lotions (single dose)	Less than 300 mg	10
	300 mg or more	7.5

3.13 Uniformity of Weight

On the word of IP this test is apposite for eye ointments. Select a sample of 10 filled containers and remove any labeling 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. Dry and again weigh each empty container together with its parts which may have been removed. The difference between the two weights is the net weight of the contents of the container [50].

In line with IP, the average net weight of the contents of the 10 containers is not less than the labeled amount and the net weight of the contents of any single containers is not less than 91 percent and not more than 109 percent of the labeled amount where the labeled amount is 50 g or less, or not less than 95.5 percent and not more than 104.5 percent of the labeled amount where the labeled is more than 50 g but not more than 100 g [50].

As stated by IP, if this requirement is not met, determine the net weight of the contents of 10 additional containers. The average net weight of the contents of the 20 containers is not less than the labeled amount, and the net weight of the contents of not more than 1 of the 20 containers

is less than 91 percent or more than 109 percent of the labeled amount where the labeled amount is 50 g or less than 95 percent or more than 104.5 percent of the labeled amount is more than 50 g but not more than 100 g [50].

3.14 Bacterial Endotoxins

Endotoxins are the toxins which cannot diffuse through the bacterial cell wall and are retained within the bacteria. They are released only when the cells die and start disintegrating [51]. The test for bacterial endotoxins (BET) measures the concentration of bacterial endotoxins that may be present in the sample or on the article to which the test is applied using a lysate derived from the hemolymph cells or amoebocytes of the horseshoe crab, *Limulus polyphemus*. Other species of horseshoe crab namely *Tachypleus gigas*, *Tachypleus tridentatus* and *Carcinoscropius rotundicauda* also yield amoebocyte lysate having similar activity [50].

The addition of a solution containing endotoxins to a solution of the lysate produces turbidity, precipitation or gelation of the mixture. However, addition of a chromogenic substrate to a solution of the lysate results in development of color due to release of chromophore from the substrate upon activation by the endotoxin present in the solution. The rate of reaction depends on the concentration of endotoxin, the pH and the temperature. The reaction requires the presence of certain bivalent cations, a clotting cascade enzyme system and clottable protein, all of which are provided by the lysate [50].

According to BP, There are 3 techniques for this test: the gel- clot technique, which is based on gel formation; the turbidimetric technique, based on the development of turbidity after cleavage of an endogenous substrate; and the chromogenic technique, based on the development of color after cleavage of a synthetic peptide-chromogen complex [30]. The following 6 methods are described in the BP [49]:

- Method A. Gel-clot method: limit test
- Method B. Gel-clot method: quantitative test
- Method C. Turbidimetric kinetic method
- Method D. Chromogenic kinetic method
- Method E. Chromogenic end-point method
- Method F. Turbidimetric end-point method

According to IP, the following methods can be used to monitor the endotoxin concentration in a product official in the pharmacopoeia and to determine whether the product complies with the limit specified in the monograph [50].

- Method A: Gel-Clot Limit Test Method
- Method B: Semi-quantitative Gel-Clot Method
- Method C: Kinetic Turbidimetric Method
- Method D: Kinetic Chromogenic Method
- Method E: End-Point Chromogenic Method

On the word of IP, when a monograph includes a test for bacterial endotoxins without mentioning a method, the test is carried out by Method A. Any one of the other four methods may be employed as an alternative method provided it yields results of equivalent reliability with the preparation under examination [50].

Consistent with IP, carry out the following procedure in receptacles such as tubes, vials or wells of micro-titre plates. Into each of the chosen receptacle, add an appropriate volume of negative control (NC), control standard endotoxin (CSE) solutions in water BET, test solution and positive product control (PPC). At intervals that will permit the reading of each result, add to each receptacle an equal volume of the appropriately constituted lysate unless single test vials are used. Mix the sample-lysate mixture gently and place in an incubating device such as a water-bath or a heating block, accurately recording the time at which the receptacles are so placed. Incubate each receptacle at 37°± 1° undisturbed for 60 ± 2 minutes. Remove the receptacles and examine the contents carefully. A positive reaction is characterised by the formation of a firm gel that retains its integrity when inverted through 180° in one smooth motion. Record this result as positive (+). A negative result is characterised by the absence of such a gel or by the formation of a viscous gel that does not maintain its integrity. Record such a result as negative (–). Handle the receptacles with care to avoid subjecting them to unwanted vibrations as false negative observations may result [34]. Consistent with IP, calculate the geometric mean end-point concentration of solutions of series B and C (Table 7) by using the following formula [50]:

$$\text{Geometric mean end-point concentration} = \text{antilog}\ (\sum e/f)$$

where, $\sum e$ = sum of the log end-point concentrations of the series of dilutions used; f = number of replicate test-tubes. This average

gives the estimated lysate sensitivity which must lie between 0.5λ and 2λ [34,49,50].

The possibility of interference with the bacterial endotoxins test by certain factors should be borne in mind. For validation of the test results it must be demonstrated that the test preparation does not inhibit or enhance the reaction or otherwise interfere with the test. The validation must be repeated if the lysate vendor or the method of manufacture or the formulation of the sample is changed. Dilution of the test preparation with water BET is the easiest method for overcoming inhibition [31]. The allowable dilution level or Maximum Valid Dilution (MVD) is dependent on the concentration of the product, the endotoxin limit for the product and the lysate sensitivity. It is calculated by the following expression [49,50]:

MVD = Endotoxin limit × Concentration of the test solution*/λ

where, λ is the labeled sensitivity of the lysate (EU/ml) [49,50].

Note: *Concentration of the test solution is expressed as mg/ml in case the endotoxin limit is specified by weight (EU/mg), or as Units/ml in case the endotoxin limit is specified by Unit (EU/Unit), or as 1.0 ml/ml in case the endotoxin limit is specified by volume (EU/ml) [50].

According to BP the geometric mean end-point concentrations of solutions B and C (Table 8) are determined. The test for interfering factors must be repeated when any changes are made to the experimental conditions that are likely to influence the result of the test [49].

Table 7. In line with IP, preparation of solutions for gel-clot techniques [50]

Solution	Final concentration of added CSE in the solution	Number of replicates
A = Solution of the product at a dilution at or below MVD (test solution)	–	4
B = Test solution spiked with indicated CSE concentrations (Positive Product Control; PPC)	21	4
	0.51	4
	0.251	4
C = Standard solution with indicated CSE concentrations in water BET	21	4
	1	2
	0.51	2
	0.251	2
D = Water BET(Negative Control; NC)	–	2

Table 8. Based on USP and BP, preparation of solutions for gel-clot techniques [34,49]

Solution	Endotoxin concentration/ Solution to which endotoxin is added	Diluent	Dilution factor	Endotoxin concentration	Number of replicates
A	None/sample solution	–	–	–	4
B	2λ/Sample solution	Test solution	1	2λ	4
			2	1λ	4
			4	0.5λ	4
			8	0.25λ	4
C	2λ/Water for BET	Water for BET	1	2λ	2
			2	1λ	2
			4	0.5λ	2
			8	0.25λ	2
D	None/Water for BET	–	–	–	2

where, Solution A: Sample solution of the preparation under test that is free of detectable endotoxins; Solution B: Test for interference; Solution C: Control for labeled lysate sensitivity; Solution D: Negative control (water for BET)

The test is considered valid when all replicates of solutions A and D show no reaction and the result of solution C confirms the labeled lysate sensitivity. If the sensitivity of the lysate determined with solution B is not less than 0.5l and not greater than 2l, the test solution does not contain interfering factors under the experimental conditions used. Otherwise, the test solution interferes with the test [49].

If the preparation being examined interferes with the test at a dilution less than the MVD, repeat the test for interfering factors using a greater dilution, not exceeding the MVD. The use of a more sensitive lysate permits a greater dilution of the preparation being examined and this may contribute to the elimination of interference [49].

Interference may be overcome by suitable validated treatment, such as filtration, neutralization, dialysis or heat treatment. To establish that the treatment chosen effectively eliminates interference without loss of endotoxins, repeat the test for interfering factors using the preparation being examined to which the standard endotoxin has been added and which has then been submitted to the chosen treatment [49].

Consistent with IP, the test for interfering factors is valid if [50]:

- Solutions of series A and D give negative results [50];
- The results obtained with solutions of series C confirm the labeled sensitivity of the lysate [50];
- The geometric mean of the end-point concentration of solutions of series B is not more than 2l or not less than 0.5l [50].

If the result obtained is outside the specified limit, the test preparation under examination is acting as an inhibitor or activator. The interfering factors may be eliminated by further dilution (not greater than MVD), filtration, neutralisation, inactivation or by removal of the interfering substances. The use of a more sensitive lysate permits the use of greater dilution of the preparation under examination [50].

Ultrafiltration may be used, if necessary, when the interfering factor passes through a filter with a nominal separation limit corresponding to a molecular weight of 10,000 to 20,000, such as asymmetrical membrane filters of cellulose triacetate. Such filters should be checked for the presence of any factors causing false positive results. The material retained on the filter, which contains the endotoxins, is rinsed with water BET or tris-chloride buffer pH 7.4 BET. The endotoxins are recovered in the water BET or the buffer. The endotoxin concentration in the test volume and the final volume are determined for each preparation under examination [50].

Establish that the chosen treatment effectively eliminates interference without removing endotoxins by repeating the test for interfering factors using the preparation under examination to which the CSE has been added and which has been submitted to the chosen treatment [50].

The product under examination complies with the bacterial endotoxin test if the positive product control is positive and the negative controls as well as the test solutions are negative. The test is not valid if the positive product control is negative or if the negative control is positive. The product under examination meets the requirements of the test if the endotoxin content is less than the endotoxin limit stated in the individual monograph. If a positive result is found for one of the test solution duplicates and a negative result for the other, the test may be repeated as described above. The results of the retest should be interpreted as for the initial test [50].

3.15 Sterility Test

Sterility is defined as the absence of viable microbial contamination. Sterility is an absolute requirement of all ophthalmic formulations. Contaminated ophthalmic formulations may result in eye infections that could ultimately cause blindness, especially if the *Pseudomonas aeruginosa* microbe is involved. Therefore, ophthalmic formulations must be prepared in a laminar flow hood using aseptic techniques just the same as intravenous formulations. The sterile formulations must be packaged in sterile containers [52].

As stated by USP and BP the sterility test may be carried out using the technique of membrane filtration or by direct inoculation of the culture media with the product to be examined. Appropriate negative controls are included [34,49].

The following culture media have been found to be suitable for the test for sterility. Fluid thioglycollate medium is primarily intended for the culture of anaerobic bacteria; however, it will

also detect aerobic bacteria. Soya-bean casein digest medium is suitable for the culture of both fungi and aerobic bacteria [34,48,49].

3.15.1 Membrane filtration

The technique of membrane filtration is used whenever the nature of the product permits, that is, for filterable aqueous preparations, for alcoholic or oily preparations and for preparations miscible with or soluble in aqueous or oily solvents provided these solvents do not have an antimicrobial effect in the conditions of the test [49]. According to BP, use membrane filters having a nominal pore size not greater than 0.45 µm whose effectiveness to retain micro-organisms has been established. Cellulose nitrate filters, for example, are used for aqueous, oily and weakly alcoholic solutions and cellulose acetate filters, for example, for strongly alcoholic solutions. Specially adapted filters may be needed for certain products, e.g. for antibiotics [49].

The technique described below assumes that membranes about 50 mm in diameter will be used. If filters of a different diameter are used the volumes of the dilutions and the washings should be adjusted accordingly. The filtration apparatus and membrane are sterilized. The apparatus is designed so that the solution to be examined can be introduced and filtered under aseptic conditions; it permits the aseptic removal of the membrane for transfer to the medium [49].

3.15.1.1 Aqueous solutions

Consistent with BP, if appropriate, transfer a small quantity of a suitable, sterile diluent such as a 1 g/L neutral solution of meat or casein peptone pH 7.1 ± 0.2 onto the membrane in the apparatus and filter. The diluent may contain suitable neutralizing substances and/or appropriate inactivating substances for example in the case of antibiotics [49].

Transfer the contents of the container or containers to be tested to the membrane or membranes, if necessary after diluting to the volume used in the method suitability test with the chosen sterile diluent but in any case using not less than the quantities of the product to be examined prescribed in Table 9. Filter immediately. If the product has antimicrobial properties, wash the membrane not less than 3 times by filtering through it each time the volume of the chosen sterile diluent used in the method suitability test. Do not exceed a washing cycle of 5 times 100 mL per filter, even if during the method suitability test it has been demonstrated that such a cycle does not fully eliminate the antimicrobial activity. Transfer the whole membrane to the culture medium or cut it aseptically into 2 equal parts and transfer one half to each of 2 suitable media. Use the same volume of each medium as in the method suitability test. Alternatively, transfer the medium onto the membrane in the apparatus. Incubate the media for not less than 14 days [49].

Table 9. In accordance with USP, JP and BP minimum quantity to be used for each medium [34,48,49]

Quantity per container	Minimum quantity to be used for each medium unless otherwise justified and authorized
Liquids (other than antibiotics)	
Less than 1 mL	The whole contents of each container
1–40 mL	Half the contents of each container, but not less than 1 mL
Greater than 40 mL, and not greater than 100 mL	20 mL
Greater than 100 mL	10% of the contents of the container, but not less than 20 mL
Antibiotic liquids	1 mL
Other preparations soluble in water or in isopropyl myristate	The whole contents of each container to provide not less than 200 mg
Insoluble preparations, creams, and ointments to be suspended or emulsified	Use the contents of each container to provide not less than 200 mg
Solids	
Less than 50 mg	The whole contents of each container
50 mg or more, but less than 300 mg	Half the contents of each container, but not less than 50 mg
300 mg–5 g	150 mg
Greater than 5 g	500 mg

3.15.1.2 Soluble solids

In line with BP, use for each medium not less than the quantity prescribed in Table 9 of the product dissolved in a suitable solvent such as the solvent provided with the preparation, water for injections, saline or a 1 g/L neutral solution of meat or casein peptone and proceed with the test as described above for aqueous solutions using a membrane appropriate to the chosen solvent [49].

3.15.1.3 Oils and oily solutions

Along with BP, use for each medium not less than the quantity of the product prescribed in Table 9. Oils and oily solutions of sufficiently low viscosity may be filtered without dilution through a dry membrane. Viscous oils may be diluted as necessary with a suitable sterile diluent such as isopropyl myristate shown not to have antimicrobial activity in the conditions of the test. Allow the oil to penetrate the membrane by its own weight then filter, applying the pressure or suction gradually. Wash the membrane at least 3 times by filtering through it each time about 100 mL of a suitable sterile solution such as 1 g/L neutral meat or casein peptone containing a suitable emulsifying agent at a concentration shown to be appropriate in the method suitability test, for example polysorbate 80 at a concentration of 10 g/L. Transfer the membrane or membranes to the culture medium or media or vice versa as described above for aqueous solutions, and incubate at the same temperatures and for the same times [49].

3.15.1.4 Ointments and creams

In relation to BP, use for each medium not less than the quantities of the product prescribed in Table 9. Ointments in a fatty base and emulsions of the water-in-oil type may be diluted to 1 percent in isopropyl myristate as described above, by heating, if necessary, to not more than 40 °C. In exceptional cases it may be necessary to heat to not more than 44°C. Filter as rapidly as possible and proceed as described above for oils and oily solutions [49].

3.15.2 Direct inoculation of the culture medium

In line with BP, transfer the quantity of the preparation to be examined prescribed in Table 9 directly into the culture medium so that the volume of the product is not more than 10 percent of the volume of the medium, unless otherwise prescribed [33]. If the product to be examined has antimicrobial activity, carry out the test after neutralising this with a suitable neutralising substance or by dilution in a sufficient quantity of culture medium. When it is necessary to use a large volume of the product it may be preferable to use a concentrated culture medium prepared in such a way that it takes account of the subsequent dilution. Where appropriate, the concentrated medium may be added directly to the product in its container [49].

3.15.2.1 Oily liquids

According to USP, JP and BP use media to which have been added a suitable emulsifying agent at a concentration shown to be appropriate in the method suitability test, for example polysorbate 80 at a concentration of 10 g/L [34,48,49].

3.15.2.2 Ointments and creams

As stated by USP, JP and BP prepare by diluting to about 1 in 10 by emulsifying with the chosen emulsifying agent in a suitable sterile diluent such as a 1 g/L neutral solution of meat or casein peptone. Transfer the diluted product to a medium not containing an emulsifying agent [34,48,49].

Incubate the inoculated media for not less than 14 days. Observe the cultures several times during the incubation period. Shake cultures containing oily products gently each day. However when fluid thioglycollate medium is used for the detection of anaerobic micro-organisms keep shaking or mixing to a minimum in order to maintain anaerobic conditions [34,48,49].

3.15.2.3 Solids

According to USP, transfer a quantity of the product in the form of a dry solid (or prepare a suspension of the product by adding sterile diluent to the immediate container), corresponding to not less than the quantity indicated in Tables 9 and 10. Transfer the material so obtained to 200 mL of Fluid Thioglycollate Medium, and mix. Similarly, transfer the same quantity to 200 mL of Soybean–Casein Digest Medium, and mix. Proceed as directed above [49]. In line with USP and BP at intervals during the incubation period and at its conclusion, examine the media for

Table 10. Consistent with USP, JP and BP minimum number of articles to be tested in relation to the number of articles in the batch [34,48,49]

Number of items in the batch*	Minimum number of items to be tested for each medium unless otherwise justified and authorized#
Not more than 200 containers	5 percent or 2 container, whichever is greater
More than 200 container	10 container
Not more than 100 containers+	10% or 4 containers, whichever is the greater
More than 100 but not more than 500 containers+	10 containers
More than 500 containers+	2% or 20 containers, whichever is less

+If the product is presented in the form of single-dose containers.
**If the batch is not known, use the maximum number of items prescribed.*
#If the contents of one container are enough to inoculate the 2 media, this column gives the number of containers needed for both the media together

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 readily determined by visual examination, 14 days after the beginning of incubation transfer portions (each not less than 1 mL) of the medium to fresh vessels of the same medium and then incubate the original and transfer vessels for not less than 4 days [34,49].

If no evidence of microbial growth is found, the product to be examined complies with the test for sterility. If evidence of microbial growth is found the product to be examined does not comply with the test for sterility, unless it can be clearly demonstrated that the test was invalid for causes unrelated to the product to be examined. The test may be considered invalid only if one or more of the following conditions are fulfilled [34,49]:

- The data of the microbiological monitoring of the sterility testing facility show a fault [34,49];
- A review of the testing procedure used during the test in question reveals a fault [34,49];
- Microbial growth is found in the negative controls [34,49];
- After determination of the identity of the micro-organisms isolated from the test, the growth of this species or these species may be ascribed unequivocally to faults with respect to the material and or the technique used in conducting the sterility test procedure [34,49].

If the test is declared to be invalid it is repeated with the same number of units as in the original test. If no evidence of microbial growth is found in the repeat test the product examined complies with the test for sterility. If microbial growth is found in the repeat test the product examined does not comply with the test for sterility [34,49].

4. CONCLUSION

QC is an essential part of the manufacturing of ophthalmic pharmaceuticals. It represents the control of the superiority of a product quality. If the quality of a product is not maintained properly, then it is tough for the product to survive in the market. To conform the requirements of ophthalmic pharmaceuticals during manufacturing QC tests are completed as per pharmacopoeial standards and specifications with a view to remove error or if necessary to adjust the process. Every test is distinctive and delivers comprehensive evaluation of QC for ophthalmic pharmaceuticals to promote the quality of pharmaceuticals for the betterment of public health.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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