Ophthalmic preparations

Definition

Ophthalmic preparations (eye preparations) are sterile, liquid, semi-solid, or solid preparations that may contain one or more active pharmaceutical ingredient(s) intended for application to the conjunctiva, the conjunctival sac or the eyelids.

The choice of base and any excipients used for the preparation of ophthalmic preparations must be proven through product development studies not to affect adversely either the stability of the final product or the availability of the active ingredients at the site of action. The addition of colouring agents is not recommended.

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

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

Manufacture

The manufacturing processes should meet the requirements of Good Manufacturing Practices, especially with regard to cross-contamination. The following information is intended to provide very broad guidelines concerning the main steps to be followed during production, indicating those that are the most important.

Throughout manufacturing, certain procedures should be validated and monitored by carrying out appropriate in-process controls. These should be designed to guarantee the effectiveness of each stage of production. In-process controls during production of ophthalmic preparations should include monitoring environmental conditions (especially with respect to particulate and microbial contamination), pyrogens (use of a limulus amoebocyte lysate (LAL) test may be advantageous), pH and clarity of solution, and integrity of container (absence of leakage, etc.). Appropriate limits should be set for the particle size of the active ingredient(s).

It is essential that ophthalmic preparations are sterile. An aseptic manufacturing process is usually employed when the dosage form does not allow routine sterilization methods to be used.[1]

[1] 5.8 Methods of sterilization

Packaging must be adequate to protect ophthalmic preparations from light, moisture, microbial contamination, and damage due to handling and transportation.

Visual inspection

Inspect the ointments, aqueous or oily solution, suspensions, or emulsions.

Evidence of physical and/or chemical instability is demonstrated by noticeable changes in colour and odour.

Sterility

Ophthalmic preparations comply with 3.2 Test for sterility.

Particle size

Ophthalmic preparations containing dispersed solid particles comply with the following test.

Take a quantity of the preparation (shake the container gently if necessary) corresponding to at least 10µg of solid active ingredient and place in a counting cell or spread in a thin layer on a slide. Firmly apply a cover-glass and scan the whole area of the sample under a microscope.[1]

[1] For practical reasons, the whole sample is first scanned at low magnification (e.g. × 50) and particles >25µm are identified. The larger particles can then be measured at a higher magnification (e.g. ×200-×500).

For each 10µg of solid active substance not more than 20 particles should have a maximum dimension greater than 25µm and not more than two of these particles should have a maximum dimension greater than 50µm. None of the particles should have a maximum dimension greater than 90µm.

Containers

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

Labelling

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

The label should include:

(1) the name of the pharmaceutical product;

(2) the name(s) of the active ingredient(s); International Nonproprietary Names (INN) should be used wherever possible;

(3) the concentration(s) of the active ingredient(s) and the amount or the volume of preparation in the container;

(4) the batch (lot) number assigned by the manufacturer;

(5) the expiry date, the utilization period, and, when required, the date of manufacture;

(6) any special storage conditions or handling precautions that may be necessary;

(7) if applicable, the period of use after opening the container;

(8) directions for use, warnings and precautions that may be necessary;

(9) the name and address of the manufacturer or the person responsible for placing the product on the market;

(10) if applicable, the name(s) and concentration(s) of antimicrobial agent(s) and/or antioxidant(s) incorporated in the preparation; and

(11) the statement "This preparation is sterile".

Storage

Ophthalmic preparations should maintain their integrity throughout their shelf-life when stored at the temperature indicated on the label. Special storage recommendations or limitations are indicated in individual monographs.

Requirements for specific types of ophthalmic preparations

Ophthalmic drops

Definition

Ophthalmic drops (eye drops) are sterile aqueous or oily solutions, suspensions, or emulsions intended for instillation into the conjunctival sac.

Ophthalmic drops should be clear and practically free from particles when examined under suitable conditions of visibility.

"Water for injections" should be used in the manufacture of aqueous ophthalmic drops.

The preparation of aqueous ophthalmic drops requires careful consideration of the need for isotonicity, a certain buffering capacity, the desired pH, the addition of antimicrobial agents and/or antioxidants, the use of viscosity-increasing agents, and the choice of appropriate packaging.

Ophthalmic drops are considered isotonic when the tonicity is equal to that of a 0.9% solution of sodium chloride. The eye can usually tolerate solutions equivalent to 0.5-1.8% of sodium chloride.

Ideally, the pH of ophthalmic drops should be equivalent to that of tear fluid, which is 7.4. However, the decision to add a buffering agent should be based on stability considerations. The pH selected should be the optimum for both stability of the active pharmaceutical ingredient and physiological tolerance. If a buffer system is used, it must not cause precipitation or deterioration of the active ingredient. The influence on the lachrymal flow should also be taken into account.

Visual inspection

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

Containers

Ophthalmic drops are normally supplied in suitable multidose containers that allow successive drops of the preparation to be administered. The container should be fitted with a tamper-evident device. The maximum volume of the preparation in such a container should be no more than 10 mL, unless otherwise specified and authorized. Multidose ophthalmic drop preparations may be used for up to 4 weeks after the container is initially opened. Droppers supplied separately should also comply with 3.2 Test for sterility.

Ophthalmic drops may also be provided in suitable single-dose containers that will maintain the sterility of the contents and the applicator up to the time of use.

It is recommended that single-dose containers for surgical use should not include any antimicrobial agents.

Ophthalmic emulsions

Definition

Ophthalmic emulsions are generally dispersions of oily droplets in an aqueous phase. There should be no evidence of breaking or coalescence.

Ophthalmic suspensions

Definition

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

Visual inspection

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

Ophthalmic ointments

Definition

Ophthalmic ointments are sterile, homogeneous, semi-solid preparations intended for application to the conjunctiva or the eyelids.

They are usually prepared from non-aqueous bases, e.g. soft paraffin (Vaseline), liquid paraffin, and wool fat. They may contain suitable additives, such as antimicrobial agents, antioxidants, and stabilizing agents.

Organoleptic inspection

Evidence of physical instability is demonstrated by:

- a noticeable change in consistency, such as excessive "bleeding" (separation of excessive amounts of liquid) or formation of agglomerates or grittiness;

- discoloration;

- emulsion breakdown;

- crystal growth;

- shrinking due to evaporation of water; or

- evidence of microbial growth.

Uniform consistency

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

Containers

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

Suitable single-dose containers may also be used.