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TO REVIEW ON OPTHALMIC PREPARATION OF EYE

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ABSTRACT

Ophthalmic preparations are sterile liquid, semi-solid, or solid preparations intended for application to the conjunctiva, the conjunctival sac, or the eyelids. Sterility is a key issue in manufacture and use of ophthalmic products. Preservative selection is a critical activity in product design. Other important aspects requiring assessment in the manufacture of ophthalmic products include sterility, tonicity, pH, buffering, drug toxicity, solubility, stability, viscosity, aseptic filling, packaging and storage. Microbial content or bioburden of the raw materials, in-process intermediates, and drug substance or active product ingredient are potential sources of contamination and require incoming testing of ingredients. Most ophthalmic products are sterilized by aseptic filtration through a 0.22µm filter. Preservatives in the ophthalmic solution will, to varying degrees, bind or be adsorbed onto many common membrane filter materials. Most commercial liquid ophthalmic products are packaged in plastic containers fitted with nozzles for drop wise administration. Plastic containers are generally sterilized by gamma irradiation or ethylene oxide. Facilities used to prepare ophthalmic preparations are required to operate within a controlled environment using HEPA filtration to minimize contact of airborne contamination with critical sites such as open product prior to application of closures, injection ports, and vial septa. Aseptic filling ophthalmic medications is typically achieved through the use of blow-fill-seal (BFS) technology in which product containers are formed from plastic granules on-line and then filled with drug solution and sealed in one

operation. Blow-fill-seal-technology has a theoretically lower risk of microbial contamination compared with conventional aseptic filling. Quality control of these products includes traditional tests such as identification, potency, purity, impurities, sterility, and particulate matter and performance tests such as dissolution or drug release. Physical or chemical instability will be demonstrated by noticeable changes in the dosage form such as changes in color, consistency, agglomerates, grittiness, emulsion breakdown, crystal growth, shrinking due to evaporation of water, or evidence of microbial growth. The finished product must also be subject to the sterility test and endotoxin tests.

INTRODUCTION

Ophthalmic preparations (eye preparations) are sterile liquid, semi-solid, or solid preparations that may contain one or more active pharmaceutical ingredients. Ophthalmic products are intended for application to the conjunctiva, the conjunctival sac, or the eyelids. The course of treatment may extend during several days. Although eye preparations contain a preservative, there is a probability of microbial contamination after the package sterility seal has been broken during the period of use.

These forms of medication must be administered directly to the eye because many of the ingredients such as peptides, proteins, and chemotherapeutic agents would be inactivated in the gastrointestinal tract if they were taken orally. The issue of overriding importance in relation to the preparation of all ophthalmic dosage forms is that they are sterile.

This paper considers the key elements relating to the manufacture of ophthalmic products from the perspective of microbial contamination control. Its focus is upon the aseptic dispensing of the products and environmental and technological requirements including blow-fill-seal filling and container sealing systems.

Two of the largest challenges faced when using topicals to treat pathological states of the eye include patient compliance and ineffective absorbance of drugs into the cornea] In fact, researchers in this field of drug delivery agree that less than 7% of drugs delivered to the eye reach and penetrate the corneal barrier, therefore, increasing the frequency of dosing used for topicals. This is one of the fundamental problem associated with using topicals to deliver drugs to the cornea and therefore leads to the increased demand for patient compliance. Together, these two factors drive a need in the field of scientific research and engineering for a way to better deliver drugs to the cornea of the eye while decreasing dosing frequency and

demand for patient compliance. Moreover, besides the logistical problems associated with using topicals, there are also systemic side effects which result from the administration of some drugs used to combat the pathological states of the eye. With the increased concentration of drugs in topicals and the frequent application to the eye, a majority of the drug is drained from the eye via nasolacrimal drainage. This drainage is thought to be the reason that systemic side effects exist from such administration.

Oxygen permeability is another important feature of all contact lenses and much be optimized to the largest degree possible when creating drug delivery devices for the eye. The contact lens adheres to the external cornea of the eye which is made up of a layer of cells. Cells, being the basic component of living organisms, require sustained and constant access to oxygen in order to survive. The cornea of the eye is not supplied with blood as are most other cells in the body, making this a challenging part of the body to which to deliver drugs. Decreasing oxygenation to the eye can result in undesirable side effects. Researchers in this field have noted that different types of contact lenses have varying degrees of oxygen permeability. For example, it has been shown that SCLs have limited oxygen permeability while silicon-based contact lenses have much better oxygen permeability] Silicon-base contact lenses have also been shown to have some other very important physical parameters.

Researchers have attempted to make the thickness of the contact lenses in order to increase the drug loading capacity of the contact lens. However, for silicon-based lenses this parameter is inversely proportion to oxygen permeability (i.e. as thickness of the contact lens increases the oxygen permeability decreases). Moreover, it has been shown that as water content increases in silicon-based lenses, the oxygen permeability decreases, another relationship that is inversely proportional. Surprisingly, as SCLs increase with water content the oxygen permeability also increases(a directly proportional relationship).

In regards to whether silicon-based lenses or SCLs are a better candidate as an ophthalmic drugdelivery device is a question that remains unanswered and is not uniformly agreed upon in the scientific community. For example, Ciolino et al. claim that silicon-based contact lenses are better candidates for patients that are long-term contact lens wearer Conversely, Kim et al. suggest that SCLs are better candidates because they show the possibility to be able to overcome the difficult of oxygen permeability as well as mechanical integrity of the lens. Kim et al. have shown that the mechanical strength can be increased for SCLs by incorporating a nanodiamond (ND) infrastructure into contact lens matrix.

AIM

To study ophthalmic preparations.

OBJECTIVES

- To understand about ophthalmic preparations
- To know about types of ophthalmic preparations
- To understand the manufacture of ophthalmic preparations
- To know the stability of ophthalmics

Ganeral Innformation

Eye drops or eyedrops are liquid drops applied directly to the surface of the eye, particularly the human eye, usually in small amounts such as a single drop or a few drops. Eye drops usually contain saline to match the salinity of the eye. Drops containing only saline and sometimes a lubricant are often used as artificial tears to treat dry eyes or simple eye irritation such as itching or redness. Eye drops may also contain one or more medications to treat a wide variety of eye diseases. Depending on the condition being treated, they may contain steroids, antihistamines, sympathomimetics, beta receptor blockers, parasympathomimetics, parasympatholytics, prostaglandins, nonsteroidal antiinflammatory drugs (NSAIDs), antibiotics, antifungals, or topical anesthetics.

These eye drops are packaged for single use, without preservatives

Eye drops have less of a risk of side effects than do oral medicines, and such risk can be minimized by occluding the lacrimal punctum (i.e. pressing on the inner corner of the eye) for a short while after instilling drops. Prior to the development of single-use pre-loaded sterile plastic applicators, eye drops were administered using an eye dropper, a glass pipette with a rubber bulb.

Advantages

- Increased residence time/bioavailability
- Precision dosing with controlled release, avoids pulsate drug delivery • Minimal systemicabsorption.
- Administration frequency reduced
- Conjunctival/scleral route to internal target
- Better shelf life and no preservatives

- Combinational therapeutic approaches

Disadvantages

- Physical and psychological obstacles of placing solid objects on the eye, forcign body sensation
- Movement around the eye could interfere with vision
- Potential accidental loss
- Some devices difficult to insert or remove
- Potential burst release upon insertion prior to controlled delivery

REGULATORY AND COMPENDIAL REQUIREMENTS FOR OPHTHALMIC PREPARATIONS

The European Pharmacopoeia does not include any specific chapters on the manufacture of ophthalmic preparations, although the monograph on eye preparations includes a short section on production (01/2008:1163). However, guidance is provided in the United States Pharmacopoeia in the form of USP general chapter Ophthalmic Ointments. This chapter addresses some of the parameters and characteristics relating to the preparation of ophthalmics, such as added substances, containers, metal particles and leakage.[3] In the future, the performance tests (dissolution and drug release) for ophthalmic preparations will included in a new general chapter titled Ophthalmic Preparations— Performance Tests <1771>. This is intended for issue in 2015.

In addition, there are a number of guidelines available in relation to aseptic filling, the usual method of preparation of ophthalmic dosage forms. Aseptic processing is highly regulated and there is considerable guidance in the US Code of Federal Regulations (CFR 21, such as CFR 21 Sub-part C (211.42)), FDA documents, and in the EU GMP "Rules and Guidance for Pharmaceutical Manufacturers and Distributors".[4] Nonetheless, regulatory guidance is limited to the basic principles expected of pharmaceutical manufacture. There are aspects which are open to interpretation or that become part of current Good Manufacturing Practice (cGMP).

With aseptic filling, the principal sources of guidance are

- FDA Guidance for Industry 2004 on Drug Products Produced by Aseptic Processing
- USP <1116> Microbiological Control and Monitoring of Aseptic Processing Environments

- ISO 13408 Aseptic Processing of Healthcare Products
- ISO 14698-1. Cleanrooms and associated controlled environments–Biocontamination Control': Part1: 'General principles and methods
- ISPE Baseline Guide to Sterile Manufacturing Facilities

MANUFACTURE

There are a number of important aspects that require assessment in the manufacture of ophthalmic products. These include the following[10,11]

- Sterility
- Tonicity
- pH and buffering
- Inherent toxicity of the drug
- Need for a preservative
- Solubility
- Stability in an appropriate vehicle
- Viscosity
- Aseptic filling

Packaging and storage of the finished product.

Water for Injection (WFI) should be used in the manufacture of aqueous ophthalmic drops. The above topics are discussed below.

Types of Opthalmic Preparations

Ophthalmic products include prescription and over-the counter drugs, products for the care of contact lenses, and products used in conjunction with ocular surgery. The rou tine need to compound sterile ophthalmic products is no longer required with the broad range of commercially manu factured products available today. Pharmaceutical manufacturers provide finished ophthalmic products, manufactured and tested for quality according to stringent industrial and government standards. The methods of sterilization include moist heat under pressure (autoclave), dry heat, filtration, gas sterilization, and ionizing radiation. For more detail. refer Chapter 41. This section will focus on the pharmaceuti cal aspects of the various ophthalmic dosage forms encom passed by these types of products. The therapeutic uses of individual products can be found in several reference books along with the individual product's labeling (Bartlett, 2009). The reader can also refer 22nd edition of

Remington (2013) for contact lens and care products.

1 Ophthalmic solutions

The most common dosage form for delivering drugs to the eye. By definition, ingredients are completely soluble such that dose uniformity is not an issue, and there is little physical interference with vision. The principal disadvan tage of solutions is their relatively brief contact time with the drug and the absorbing tissues of the external eye. Contact time can be increased by the inclusion of viscosity-imparting agents; however, their use is limited to relatively low viscosities so as to allow dispensing of the eye drop from the container or eyedropper and to min imize excessive blurring of vision.

2 Gel-forming solutions

Ophthalmic solutions (usually water based), which contain a polymer system that is a low-viscosity liquid in the container but gels on contact with the tear fluid, have increased contact time and can provide increased drug absorption and prolonged duration of therapeutic effect. The liquid-to-gel phase transi tion can be triggered by a change in temperature, pH, ionic strength, or the presence of tear proteins, depending on the particular polymer system employed. Temperature sensitive in situ gel of azithromycin (Azasite) prepared using Poloxamer 407 is FDA approved for conjunctivitis.

Pilocarpine-Carbopol 940 (pH sensitive) in situ gel (Pilopine HS) is used to manage glaucoma (Wu et al., 2019).

3 Powders for solutions

Drugs that have very limited stability in aqueous solution can sometimes be prepared as sterile powders for recon stitution by the pharmacist before dispensing to the patient. The sterile powder should be aseptically reconsti tuted with the accompanying sterile diluent that has been optimized for dissolution, preservation, and stability. The pharmacist must convey to the patient any special storage instructions, including the expiration date.

4 Ophthalmic suspensions

Suspensions are dispersions of finely divided, relatively insoluble drug substances in an aqueousvehicle contain ing suitable suspending and dispersing agents. The vehicle is, among other things, a saturated solution of the drug substance. Because of a tendency of particles to be retained in the culde- sae, the contact time and duration of action of a suspension could

theoretically exceed that of a solution. The drug is absorbed from solution, and the solution concentration is replenished from retained parti cles. Each of these actions is a function of particle size, with solubility rate being favored by smaller size and retention favored by a larger size; thus optimum activity should result from optimum particle size. For aqueous suspensions the parameters of intrinsic solubility and dissolution rate must be considered. Particle size also plays an important part in the irritation potential of the dosing system. This consideration is important, because irritation produces excessive tearing and rapid drainage of the instilled dose, as discussed earlier. It has been recom mended that particles be smaller than 10 μm to minimize irritation to the eye.

5 Ophthalmic ointments

Ophthalmic ointments are primarily anhydrous and contain mineral oil and white petrolatum as the base ingredients, the proportions of which can be varied to adjust consistency and the melting temperature. Dosage variability is greater than with solutions (though probably no greater than that with suspensions). Ointments will interfere with vision, and their use is usually limited to bedtime instillation. They remain popular as a pediatric dosage form and for postoper ative use. The anhydrous nature of the base enables its use as a carrier for moisture-sensitive drugs. The petrolatum base can be made more miscible with aqueous components by the addition of liquid lanolin Ointments do offer the advantage of longer contact time and greater total drug bio availability, albeit with slower onset and time to peak absorption. Acyclovir ocular ointment (Avaclyr) by Fera Pharmaceuticals was FDA approved in 2019 for the treat ment of acute herpetic keratitis, Ciprofloxacin-PIGA (Poly(lactic-co- glycolic acid) nanoparticle-loaded ointment showed prolong release for 10 hours for effective treatment of conjunctivitis (Jelinkova et al., 2019).

6 Ophthalmic emulsions

An emulsion dosage form offers the advantage of the abil- ity to deliver a poorly water-soluble drug in a solubilized form as an eye drop. The drug is dissolved in a nonaque- ous vehicle, such as castor oil, and emulsified with water, using a nonionic surfactant and, if needed, an emulsion stabilizer. An emulsion with water as the external phase can be less irritating and better tolerated by the patient than the use of a purely nonaqueous vehicle. Lipid-based microemulsion to deliver hydrophobic drugs showed improved drug retention and corneal permeability. Such an emulsion is used to deliver cyclosporine topically for the treatment of chronic dry eye conditions (United States Patent No. 5).

7 Ophthalmic gels

Gel-forming polymers, such as carbomer, have been used to develop aqueous, semisolid dosage forms that are packaged and administered the same as ointments. The viscous gels have significantly increased topical residence time and can increase drug bioavailability and decrease dosage frequency, compared to solutions. Although they contain a large proportion of water, can still cause blurring of vision. A carbomer gel of pilo- they can carpine administered at bedtime has been shown to prolong the intraocular pressure (IOP)-lowering effect patients for up to 24 hours (March et al., 1982). Brimonidine tartrate ophthalmic gel prepared using Carbopol 974P and hydroxypropyl methyl cellulose (HPMC) E4M showed a significant reduction in the intraocular pressure in comparison to eye drops (Pang et al., 2018). Refresh Celluvise preservative-free gel showed prolong effect to manage dry eyes.

8 Ocular inserts

Ocular inserts have been developed in which the drug is delivered on the basis of diffusional mechanisms. Such a solid dosage for delivers an ophthalmic drug at a near constant known rate, minimizing side effects by avoiding excessive absorption peaks. The Ocusert is designed to be placed in the lower cul-de-sac to provide a weekly dose of pilocarpine, after which the system is removed and replaced by a new one. The near zero-order rate delivery is selection of a non-eroding copolymer membrane enca ing the drug reservoir (Shell and Baker, 1974). Triamcinolone acetonideloaded polybutylene succinate oculari showed sustain release for the month. Dextenza intracanatico lar insert (FDA approved) is a preservative-free hrydege insert that delivers 0.4 mg of dexamethasone for the treaties of postsurgical ocular inflammation 30 days ste release) (Mann et al., 2018). An erodible insert is available (LACRISERT) for the treatment of the dry eye. It is molded in the shape in of a rod froma hydroxypropyl cellulose polyme which is the active ingredient. When inserted into the low cul-de- so le-suc, the polymer imbibes tear fluid and forms a gel like mass that gradually erodes while thickening the tearfi over a period of several hours. The unit-dose insert is any drous, and no preservative is required, which is beneficial for some sensitive patients.

9 Soft contact lenses

Drug delivery using soft contact lenses have become very popular due to its unique advantages suchas high bio availability, location immediate to the comes (direct absorption), high drug retention, preservative free, and easy termination (by removing contact lens) (Maulvi et al., 2016). Scientists have worked on numerous systems such as micelles,

microemulsion. liposome, polymeric nanoparticles, use of vitamin E, implantation technology. and supercritical fluid technology to prolong the drug delivery from the contact lenses. The developed therape tic contact lens showed altered critical lens properties such water content (swelling), transmittance, tensile strength, and ion and oxygen permeability, which pose the limitation to commercialize contact lenses for drug delivery. However, recent technologies have addressed scientific challenges, and currently, many therapeutic con tact lenses are under clinical studies, with the expectation to be commercialized in the next few years.

Mechanism

Different pharmacological classes of eye drops can be recognized by patients by their different colored tops. For instance, the tops to dilating drops are a different color than anti-allergy drops.

Dry eyes

Eyes drops sometimes do not have medications in them and are only lubricating and tear-replacing solutions. There is a wide variety of artificial tear eye drops that provide different surface healing strategies. One can find bicarbonate ions, hypotonicity, high viscosity gels and ointments, and nonpreserved types. They all act differently and therefore, one may have to try different artificial tearsto find the one that works the best.

Steroid and antibiotic eye drops

Steroid and antibiotic eye drops are used to treat eye infections. They also have prophylactic properties and are used to prevent infections after eye surgeries. They should be used for the entire time prescribed without interruptions. The infection may relapse if the use of the medication is stopped.

Pink eye

Antibiotic eye drops are prescribed when infection conjunctivitis is caused by bacteria but not when itis caused by a virus. In the case of allergic conjunctivitis, artificial tears can help dilute irritating allergens present in the tear film.

Allergies

Some eye drops may contain histamine antagonists or nonsteroidal anti-inflammatory drug (NSAIDs), which suppress the optical mast cell responses to allergens including (but not

limited to) aerosolized dust particles.

Glaucoma

Eye drops used in managing glaucoma help the eye's fluid to drain better and decrease the amount of fluid made by the eye which decreases eye pressure. They are classified by their active ingredient and they include: prostaglandin analogs, beta blockers, alpha agonists, and carbonic anhydrase inhibitors. There are also combination drugs available for those patients who require more than one type of medication.[6]

Mydriatic eye drops

These make the eye's pupil widen to maximum, to let an optometrist have the best view inside the eyeball behind the iris. Afterwards in sunny weather they can cause dazzling and photophobia until the effect of the mydriatic has worn off.

In some countries including Russia and Italy, Tropicamide, a mydriatic eye drop, is used to some degree as an inexpensive recreational drug.[7] Like other anticholinergics, when taken recreationally, tropicamide acts as a deliriant. When injected intravenously, as is most often the case, the tropicamide may cause problems such as slurred speech, unconsciousness, unresponsiveness, hallucinations, kidney pain, dysphoria, hyperthermia, tremors, suicidal tendency, convulsions, psychomotor agitation, tachycardia and headache.

Stability Examination

The basic requirement for drug forms applied on the eyeball is their sterility. Examination of sterility involves inoculation in aseptic conditions of the sample examined on two microbiological media: thioglycolate medium (fluid sodium mercaptoacetate or sodium thioglycolate), which is used for growth of aerobic and anaerobic bacteria, and medium with hydrolysate of casein and soy (soya-bean casein digest media) used for growth of aerobic bacteria and fungi. A thioglycolate medium with an applied sample is incubated at the temperature of 30–35°C, whereas a medium with hydrolysate of casein and soy with an applied sample is incubated at the temperature of 20–25°C for the time not shorter than 14 days. Two methods are distinguished for inoculation of examined material: direct inoculation and a method involving use of membrane filters.

The direct inoculation method, as described in Pharmacopoeia, involves transferring the suitable amount of examined preparation to the medium. If a product has antimicrobial

properties, such effect of the substance should be neutralized before the examination. Before their introduction to the medium, the ointments should be diluted with a suitable sterile solvent containing the chosen surface active agent. During incubation, the media with introduced samples should be observed at specified time intervals.[9,55]

The indirect method (membrane filtration method) is used when the character of the product enablesit. For water and oil solutions, filters from cellulose nitrate are used in which size of pores does not exceed 0.45 m. For some products, for example, antibiotics, specifically adjusted filters are employed. In the case of testing products with antimicrobial effects, the membrane should be washed with chosen sterile solvent not less than 3 times, not exceeding the fivefold cycle of filter washing for 100 mL of solvent. The entire membrane is transferred to a suitable medium or is aseptically cut into two identical parts, which are transferred into two different media. In the case of solids soluble in water, the substance should be dissolved in a suitable solvent and the further procedure should be the same as with water solutions. The indirect method can be also used for ointments. Ointments with fatty bases can be diluted with isopropyl myristate if it is required, at the temperature not higher than 40°C. In exceptional situations, the upper temperature limit may be 44°C. Afterwards, the product is filtered as quickly as possible. For every drug form, after filtration and washing, the membrane is transferred to the medium or the medium is introduced to the filtration set on the m.

Process Controls

The microbial content or bioburden of the raw materials, in-process intermediates, and drug substance or active product ingredient is important. These materials are potential sources of contamination. Incoming testing of these ingredients are an important part of overall microbiological control and cleanliness of the manufacturing process.

Throughout manufacturing, certain procedures should be monitored by carrying out appropriate inprocess controls during the actual manufacturing process. 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 such as particulate and microbial contamination; bioburden testing, assessment of pyrogens, pH, and clarity of solution. Bacterial endotoxin contamination presents a serious theoretical risk. Use of the Limulus amoebocyte lysate (LAL) test is advantageous as an analytical tool. The integrity of the container including absence of leakage, etc., is an

important consideration. Appropriate limits should be set for the particle size of the active ingredients.

Sterile Filtration

When an ophthalmic preparation is compounded from a non-sterile ingredient, the final product must be sterilized. Sterilization by autoclaving in the final container (terminal sterilization) may be possible for some products if product stability is not adversely affected and appropriate quality control procedures are followed. In most cases, however, product stability concerns necessitate aseptic filling of product.

Prior to the aseptic filling of the ophthalmic preparations, the bulk solutions must be sterilized. Filtration of the preparation through a 0.22-µm filter into a sterile final container is the most commonly used method. Such filters can remove most bacteria and fungi, but not all viruses or mycoplasmas. Fibre-shedding characteristics of filters should be minimal. The integrity of the sterilised filter should be verified before use and should be confirmed immediately after use by an appropriate method such as a bubble point, diffusive flow, or pressure hold test.

With sterilizing filtration, care must be taken with the selection of the filter. Preservatives in the ophthalmic solution will, to varying degrees, bind or be adsorbed onto many common membrane filter materials. The degree of adsorption depends on both the preservative and the chemical composition of the filter (membrane polymer, surface chemistry, support materials, and so forth). The uptake of preservative by the filter is highest at the start of filtration and diminishes with time according to the volume of product processed relative to the membrane area. Product quality specifications should include preservative content requirements to assure sufficient preservative efficacy in the product.

Containers

Ophthalmic liquid products were traditionally packaged in glass containers fitted with an eye dropper. Today glass containers have limited use except where product stability or compatibility issues exclude the use of flexible plastic containers made of polyethylene or polypropylene. Most commercial liquid ophthalmic products are packaged in plastic containers fitted with nozzles from which, by gentle squeezing, the contents may be delivered as drops. Many ophthalmic liquids can be packaged in sterile plastic bottles with self-contained dropper tips or in glass bottles with separate droppers. Whichever container type is

selected, all containers must be adequately sealed to prevent contamination

Plastic containers are generally sterilized by gamma irradiation or ethylene oxide. Ethylene oxide sterilization and irradiation are not customarily in-house methods of sterilization used by pharmaceutical manufacturing companies; hence such items are normally purchased presterilised. The ointment base for an ophthalmic ointment may be sterilised by dry heat or more commonly by filtration at a temperature sufficiently high to ensure fluidity. Sterilized components are brought into the filling room via a pass-through hatch. Filling then proceeds in a manner similar to other types of liquid products, although the method of filling is more commonly blow-fill-seal rather than conventional aseptic filling.

The materials for containers and closures must not adversely affect the quality of the preparation. The potential for diffusion of any kind into or across the packaging material of the container into the preparation must be investigated. The final container should be appropriate for the ophthalmic product and its intended use and should not interfere with the stability and efficacy of the preparation. The container should be fitted with a closure that minimizes microbial contamination and a tamper-evident device that reveals whether the container has ever been opened.

Personnel and Training

The staff working on the process and for the filling of the product must be suitably trained and certified to work within cleanrooms. Training of personnel is a critical issue. Any activities conducted by human personnel represent a high risk for contamination. Personnel training, retraining, and ongoing monitoring of performance must be a continuing consideration in manufacturing of sterile products.

FACILITY DESIGN

The manufacturing processes for the manufacture and dispensing of ophthalmic products must be designed to avoid cross-contamination. Facilities used to prepare ophthalmic preparations are required to operate within a controlled environment to minimize contact of airborne contamination with critical sites such as open product prior to application of closures, injection ports, and vial septa.

All aseptic dispensing should be undertaken in cleanrooms. A cleanroom is any area in an aseptic process system for which airborne particulate and microorganism levels are

controlled to specific levels to the activities conducted within that environment. Air cleanliness is achieved through the use of filtered air (High Efficiency Particulate Air - HEPA - filters) and control of air movement and direction.

An ISO Class 5 environment (approximately equivalent to EU and WHO GMP Grade A or Class 100) is required for aseptic filling of ophthalmic products. To meet these requirements, HEPA-filtered airflow is used to dilute and remove airborne particles. Airflow adjustments can lead to an improvement with particle counts This is either an enclosed barrier unidirectional airflow device or within an isolator. The filling zone is located within an ISO Class 7 (EU and WHO GMP Grade B) or an ISO class 8 (EU and WHO GMP Grade C) cleanroom. The grade depends upon whether blowfill-seal technology is used.

With filling, the most critical zone is the point-of-fill location. This is the location where units of the sterile dosage form are released from the containment system which maintained their sterility in bulk into their final containers, and where these containers are sealed to ensure and maintain the sterility of their contents. Sealing is undertaken by the sealing of an ampoule by heat. The risk is greatest here because this is the moment in time when any contamination is likely to be of most significance.

With aseptic manufacture, the preparation (solution, suspension, emulsion, ointment, etc.,) of the ophthalmic product and the individual components of the container system are sterilised separately. The components are then brought together by aseptic methods which ensure that the existing sterility is not compromised. Thus aseptic filling involves the handling of sterile materials in a controlled environment in which the air supplies, materials, and equipment are regulated to control microbial and particulate contamination to acceptable levels. Aseptic filling is subject to a greater contamination risk than terminal sterilisation since the same level of sterility assurance cannot be built into the process.

Aseptic filling requires the close coordination and complex interaction between personnel, sterilized product, the fill/finish equipment system, cleanroom and support facilities, and sterilized filling components. While aseptic manufacturing facility design is complex and every facility is unique, careful consideration must be given to the design of aseptic operations. These include the class of cleanrooms, areas where the product is transferred into the aseptic processing area, and where and how the product is to be dispensed. The fundamental aspects of the design are cleanrooms and equipment. A regulatory expectation is

that risk assessment has been built into the design process.

Blow Fill Seal Technology

Aseptic filling ophthalmic medications is typically achieved through the use of blow-fill-seal (BFS) technology. Blow-fill-seal is a process where the containers are formed from plastic granules on-line and then filled and sealed in one operation. Blow-fill-seal units are purpose-built machines in which, in one continuous operation, containers are formed from a thermoplastic granulate, filled with the pharmaceutical preparation, and then sealed by a single automatic machine.[14] Blow-fill- sealtechnology has a theoretically lower risk of microbial contamination compared with conventional aseptic filling. BFS is an automated process where containers are formed, filled and sealed in a continuous operation without human intervention. This is performed in an aseptic enclosed area inside the BFS machine.

The BFS process begins with a pharmaceutical-grade plastic resin being is vertically heat-extruded through a circular throat to form a hanging tube called the parison. This extruded tube is then enclosed within a two-part mould, and the tube is cut above the mould. The mould is transferred to the filling zone or sterile filling space where filling needles mandrels are lowered and used to inflate the plastic to form the container within the mould. Following the formation of the container, the mandrel is used to fill the container with liquid. After filling, the mandrels are retracted and a secondary top mould seals the container. All activities take place inside a sterile shrouded chamber inside the machine. The product is then discharged to a non-sterile area for labelling, packaging and distribution.[15,16]

Microbial contamination of containers during BFS manufacturing is normally very low However, there are a number of variables that can influence the possibility of a container becoming contaminated.[18] These include the effects on the rate of vial contamination of systematic changes in the process variables, rate of provision of ballooning air, delay in the application of mould vacuum, and duration of transfer of the open vial. A relationship has been established between the level of airborne microorganisms in the machine operating environment and the extent of product contamination.

One advantage with blow-fill-seal products is that they are less fragile and lighter to transport than glass containers. Another advantage of the process is that the equipment is amenable to cleaning and sanitisation using automated steam-in-place systems However, sometimes the active ingredients or preservatives are absorbed by the plastic, which affects

product content and stability. Hence it is important to understand the interaction of ophthalmic antimicrobial preservatives with BFS packaging in the event that adsorption levels are high. Adsorption is a concern for both active drug and preservatives. A further potential disadvantage is that the operation can suffer many process interruptions arising from burnt containers

PRODUCT STERILITY

Aside from the demonstrable efficacy of the product, sterility is the most important issue given the route of administration of ophthalmic.[24] The manufacture of sterile products, like ophthalmics, isnot straightforward and microbial contamination control needs to play an essential role. There are severe risks for patients if sterile products become contaminated. Risks to patients with ophthalmic products include serious infection, blindness, and even death. Ocular infections and loss of vision caused by contamination of extemporaneously prepared ophthalmic products have been reported). Enhancing the probability of sterility is gained through environmental controls during manufacture – building quality into the process. Sole reliance must not be placed on the end-product sterility test. Final product sterility testing has several weaknesses including low statistical certainty of detecting contamination.

MONITORING AND CONTROL

There are a number of quality attributes that must be considered for the manufacture and release of ophthalmic products. Procedures and acceptance criteria for testing ophthalmic preparations are divided into two categories. Traditional quality control tests assess general quality attributes such as identification, potency, purity, impurities, sterility, and particulate matter. Performance tests assess in vitro product performance such as dissolution or drug release of the active drug substance from the drug product. Both quality and performance tests assure the identity, strength, quality, purity and efficacy of the drug product.

A specific and stability-indicating test should be used to determine the potency strength (content) ofthe drug product. In cases when the use of a non-specific assay test is justified, other supporting analytical procedures should be used to achieve overall specificity.

The preservative used in any ophthalmic product must be evaluated. While it is not necessary to perform testing on a batch-by-batch basis, the preservative used in each product must be assessed aspart of product development. The test must be repeated should any changes to the

formulation of either the preservative or the product occur. In addition, the test should be re-run at regular intervals. Preservatives must meet the requirements of Antimicrobial Effectiveness Testing.

The compendial Antimicrobial Effectiveness Test (AET) is essentially a suspension test designed to demonstrate the extent of microbial kill. The AET test comprises a controlled inoculum of the challenge organisms is placed in suspension with the preservative sample to be tested, and the number of survivors determined at different time points. Key aspects of the test are with developing a method for neutralisation of the preservative. Residual preservative in the recovery agar could artificially depress the recovery of viable cells. It is thus important to neutralize this residual activity to get accurate counts of survivors.

A further quality control test of importance is measurement of pH. The pH and buffering capacity of an ophthalmic preparation are important for preservation since the stability of most commonly used ophthalmic drugs is largely controlled by the pH of their environment.

Each vial of finished product must be subject to visual inspection. The inspection should focus on cracks or abrasions to the vials and evidence of any particulate matter in solution products. Suspension dosage forms containing dispersed solid particles are obviously not tested for solution clarity. The packaging system should be closed or sealed to prevent contamination or loss of contents. Evidence of physical or chemical instability will be demonstrated by noticeable changes in the dosage form. For example, change in color, change in consistency such as excessive "bleeding" (separation of excessive amounts of liquid), formation of agglomerates or grittiness, emulsion breakdown, crystal growth, shrinking due to evaporation of water, or evidence of microbial growth. The container integrity should have been validated to demonstrate that no penetration of microbial contamination or chemical or physical impurities can occur. The concern about containers extends to the outer packaging, which must be adequate to protect ophthalmic preparations from light, moisture, microbial contamination, and damage due to handling and transportation.

The finished product must also be subject to the sterility test . A second final product test of importance is the test for endotoxins. All injected ophthalmic drug products must be prepared in a manner designed to minimize bacterial endotoxins. This is examined using the Bacterial Endotoxins Test using the Limulus amebocyte lysate (LAL) methodology.

SUMMARY

This paper has presented an introductory overview to the preparation, manufacture, filling and quality assessment of ophthalmic products. Liquid ophthalmic products include a wide variety of formulations for cleaning and storing contact lenses, eye washes and drops, as well as many therapeutic treatments. Given the route of administration – into the human eye – it is important that the product is developed in such a way that it is efficacious and that it manufactured so that it is free from microbial contamination. Because few ophthalmic products can be terminally sterilised, a great deal of importance is placed around the process of aseptic filling. This paper has placed a strong emphasis upon the necessary requirements for the successful adoption of blow-fill-seal technology.

Unlike the majority of sterile products that are intended for single use, many ophthalmic medications are designed for multiple dosages. Protection from microbial growth is through the use of a microbiological preservative. In addition to the other quality attributes described, the correct formulation and assessment of the preservative is critical for the continued protection of the consumeror patient.

CONCLUSIONS

Despite many achievements in the field of ophthalmic dosage forms, still vast majority of active substances for use in ocular disorders are in the form of eye drops. Some of the more complex forms appeared on the pharmaceutical market, such as Ocusert by Alza Corporation, but scientists are still looking for the perfect ophthalmic system, which would possess desired properties such as controlled release, minimizing systemic effects, ease of use, and extended retention time at the site of application. Multicompartment systems appear to be promising drug forms that can also be combined with other forms, for example, polymeric nanoparticles with the active substance suspended in the in situ gel.

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In connection with the development of new ophthalmic dosage forms, a problem concerning the analysis of their physicochemical properties and in vitro-in vivo correlation appears. This paper is a review of the available literature which allows planning studies to be conducted on standard and modern ophthalmic drug forms.

Any research is never an individual effort it is contributory efforts of many hearts and brains. We all marvel at the beautiful rose, the rose with all its beauty and grandeur. But seldom, We

pause and thank the gardener who patiently mannered. The dissertation We have written is the fruits of many such unseen hands.

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