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Ophthalmic Ointment & Formulation: A Review

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Abstract— *Using ointments as an eye drug delivery system gives topical therapy a significant new aspect. Ointments are a great way to increase ocular contact duration and are generally safe and well-tolerated. Increased contact time results in higher drug levels in the eyes. Experimental evidence, however, suggests that corticosteroid ointments do not enter the eye as deeply as suspension solutions do. This could be related to both the specific steroid component and the drug's binding to the ointment base. Ointments can get contaminated, just like other ophthalmic preparations. It is not recommended to apply ophthalmic ointments to eyes that have open sores. It seems safe and effective to apply ointments to postoperative eyes where wound closure is secure.*

Keywords— ***Contamination-entrapment of corneal, drug-base compatibility, duration of drug contact, emulsifiers, ophthalmic ointments, and ocular penetration.***

I. INTRODUCTION

For many years, one of the most significant and extensively advanced fields of pharmaceutical science has been the development of ophthalmic medication forms. Scientists are interested in these drug forms because of the issue of the medication's low bioavailability following application to the eye. The intricate anatomical structure of the eye, the cornea's small absorptive surface and low transparency, the lipophilicity of the corneal epithelium, metabolism, enzymolysis, the drug's bonding with proteins in tear fluid, and defense mechanisms like tear production, blinking, and substance flow through the nasolacrimal duct are some of the other factors that contribute to its cause [1-3].Low conjunctival sac capacity roughly 30 μL without blinking [4]—as well as the previously stated defense mechanisms reduce the amount of medicine present in the application site and shorten the time the active component is present in the absorption site. The principal aim of creating ocular drug forms is to attain the necessary drug concentration at the site of absorption and maintain it for a suitable duration, hence leading to a reduction in the frequency of administration [1–5]. One of the first changes made to traditional ophthalmic medicine formulations was the addition of polymers, which allowed the active ingredient to come into longer contact with the ocular surface and increase its bioavailability. The next option to alter the bioavailability of the active ingredients in ophthalmic forms was to add excipients to the formulation, which improved the medication's capacity to enter the eye. Chelation agents were among these excipients inclusion complexes are made up of chelating agents, surfactants, and cyclodextrins in addition to active substances. This improves poorly soluble medicines' permeability, solubility, and bioavailability [1-4]. The more modern drug forms, such as multicompartment carrier systems, inserts, collagen shields, contact lenses, and socalled in situ gels, have been the subject of research in recent years

to produce a controlled release of drug to eyeball tissues [1-3, 5]

II. TOPICAL OPHTHALMIC DRUG FORMS

2.1. Liquid Ophthalmic Drug Forms

2.1.1Eye Drops. Eye drops are available as emulsions, suspensions of one or more active substances, and solutions of water and oil. If preserved, the suspensions may include preservatives in multipurpose containers. These are isotonic and sterile forms.The ideal pH for eye drops is approximately 7.4, which is the same as that of tear fluid.The tissue's tolerance to the preparation and the stability of the active ingredient should be considered when determining whether to buffer the medication in this form [7-9]. The patient may experience discomfort, irritation, and decreased drug absorption due to increased tearing if the pH value falls outside the eye's tolerance range of 4–8 [10].

2.1.2OphthalmicSolutions:Ophthalmic solutions are sterile, waterbased solutions that are used for a variety of purposes, including cleaning and washing the eyes.They might have excipients in them, which, for Control the preparation's viscosity, pH, and osmotic pressure, for instance. If kept in receptacles with several uses, they could additionally include preservatives [7].

2.1.3. Potential medication forms include microemulsions, which are affordable to make, simple to sterilize, and stable, allowing for the introduction of higher concentrations of active component. Research conducted in vivo and clinical examinations of well-trained subjects demonstrated longer durations of efficacy and higher bioavailability of medications administered in various forms.The drug's reservoir, nanodrops, and the inner phase of the microemulsion, which controls overflow, are adsorbed on the corneal surface as part of the mechanism of action [5].Microemulsions have been created for the following active ingredients: difluprednate [11], cyclosporine A [12], flurbiprofen axetil [13], and the prodrug of flurbiprofen.

2.1.4. Liquid Ophthalmic Dosage Form Modifications. Throughout the development of dosage form technology, numerous methods have been suggested suchbeen suggested as a way to boost the active ingredient's absorption into the eye tissues and lengthen the time liquid dosage forms are in touch with them.These adjustments include prodrugs or cyclodextrins, as well as the addition of chemicals that boost viscosity and introduce drug penetration increasing compounds into the formulation [4, 5, 7–10].

2.1.5 The addition of substances that increase adhesion and viscosity.It is possible to increase the duration of contact with the cornea and the drugs' absorption by making the formulation more viscous. These substances include high molecular weight hydrophilic polymers, which form three-dimensional networks in water and do not disperse across biological membranes. Polyvinyl alcohol, poloxamers, hyaluronic acid, carbomers, and polysaccharides—that is, cellulose derivatives—as well as gellan and xanthan gum are a few examples of these polymers. Hyaluronic acid is employed as a polymer to build a biodegradable and biocompatible matrix that allows for extended drug release times, while the previously mentioned carbomer is used in liquid and semisolid formulations as a suspending or viscosity-inducing ingredient [4, 8]. Studies have demonstrated that the highest possible When the viscosity of an eye drop solution is between 15 and 150 mPas, the maximum increase in penetration through the cornea occurs. Forming gels is an example of a "extreme" usage of chemicals that increase viscosity, as it allows for a reduction in drug application frequency to once daily. The use of synthetic polyoxyethylene-polyoxypropylene block copolymer (poloxamer 407) as a carrier in ocular formulations containing pilocarpine, which stimulates the active component, has been demonstrated to be appropriate. This formulation's primary drawback is vision blurring, which has a detrimental effect on patients' acceptance of it [4, 8]. These days, hydrophilic polymers are used in a lot of eye solutions, although more as substances with mucoadhesive qualities than as ones that thicken [4]. These forms are made up of polymers that create noncovalent bonds with conjunctival mucin. They are often macromolecular hydrocolloids with several hydrophilic groups (amide, sulfate, carboxyl, and hydroxyl) that can form electrostatic connections to maintain extended contact with the surface of the eye. The mucoadhesive dosage form exhibits a greater bioavailability when compared to other formulations [5]. Examples of polymers that have

been studied in relation to enhancing drug bioavailability and mucoadhesion in ophthalmic preparations are chitosan, polyacrylic acid, sodium carboxymethyl cellulose, and hyaluronic acid. Lectins are another type of chemical that prolongs contact with the surface of the eye. They have also been studied in relation to selective drug binding to a particular area of the cornea [4, 5, 8]. Two formulations: Pilogel and NyoGel (Novartis) with timolol maleate (Alcon Laboratories) and pilocarpine hydrochloride include cross-linked polyacrylic acids, Carbomer and Carbopol, respectively, that demonstrate mucoadhesive qualities [14]. 2.1.6. Adding Substances with Increased Penetration. The goal of utilizing penetration-enhancing compounds in ophthalmic medications is to improve corneal absorption through altering the corneal epithelium's structural continuity. Studies have indicated that chelating compounds, surfactants, bile acid salts, and preservatives (such as benzalkonium chloride) exhibit similar characteristics. These compounds, however, showed signs of local toxicity, which limited their application in the development of ophthalmic medication forms [3, 4].

2.1.7. Prescription medications. By creating prodrugs, it is also possible to change the characteristics of the medication and make it more permeable through the cornea. This process entails chemical structure, which bestows new characteristics on the active component, namely selectivity and site specificity [4]. Prodrugs were created for a variety of medicinal compounds, such as timolol, pilocarpine, phenylephrine, and adrenaline [4, 15]. Because of its six hundredfold higher lipophilicity at pH 7.2, dipivefrine, a diester of pivalic acid and epinephrine, exhibits a seventeenfold higher permeability through the cornea than epinephrine. Thus, the therapeutic impact of dipive-frine, when placed to the eyeball, is comparable to that of epinephrine at a lower dose. When compared to traditional eye drops that contain 2% epinephrine, eye drops containing 0.1% dipivefrine exhibit a somewhat reduced ability to control intraocular pressure.[15]

Cyclodextrins (2.1.8). Cyclodextrins are cyclic oligosaccharides that have the ability to combine with active ingredients to create inclusion complexes, which increases the solubility of hydrophobic substances in water without modifying their molecular structure [3, 16]. They allow hydrophobic medications to be kept in solution and transported to the surface of biomembranes as carriers. For ophthalmic medications, the ideal concentration of cyclodextrins (<15%) in an aqueous eye drop solution yields the best absorption of the active ingredient [4]. 2-hydroxypropyl-β-cyclodextrin is the most widely utilized cyclodextrin in developing forms put over the eyeball, as it does not exhibit irritating effects. Compared to conventional eye drops, eye drops with drug inclusion complexes—pilocarpine or dexamethasone with 2-hydroxypropyl-β-cyclodextrin—ensure greater bioavailability and are more tolerated [3].

2.2.Semisolid ophthalmic Drug Forms

2.2.1. Sol-to-Gel Systems or In Situ Gels. Viscous liquids known as in situ gels exhibit the capacity to change from a sol-to-gel state in response to external stimuli such as appropriate temperature, pH, and electrolyte content. This characteristic increases the bioavailability of the active ingredient and slows down the drug's drainage from the surface of the eyeball. Gellan gum, poloxamer, and cellulose acetate phthalate are among the polymers used in the development of these drug forms, while ciprofloxacin hydrochloride, timolol maleate, fluconazole, ganciclovir, and pilocarpine are among the active components used in in situ gel research [3-5, 8].

2.2.2. Creams for the eyes. Ointments are semisolid external dosage forms that are often made of a solid or semisolid hydrocarbon base with a softening or melting point that is near to body temperature of a human. The ointment breaks down into tiny drops when it is applied to the eye, staying in the conjunctival sac for a longer amount of time and therefore improving the drug's bioavailability. Eye ointments have various drawbacks—while they are safe and well-tolerated, they can occasionally cause irritation and cause blurred vision, among other things. effects, which is why they are primarily used at night [8]

2.3. Sturdy Ocular Medication Forms . 2.3.1 Drug-Coated Contact Lenses. Water-soluble chemicals can be absorbed by this medication form on its surface and released after putting the medication on the eyeball for an extended amount of

time. The cross-linked poly(2-hydroxyethyl methacrylate) with a tiny amount of ethylene glycol dimethylacrylate was the first and most commonly utilized polymer in the creation of lenses [4, 5]. Utilizing silicon-based lenses has been the subject of research in recent years [17–20]. The growing number of publications on contact lenses' use that have been published in recent years is evidence that interest in these lenses is still growing. The pharmaceutical availability of medications such as timolol [17], ciprofloxacin [18], dexamethasone [19], and cyclosporine [20] has been studied.

Ocular Inserts 2.3.2. Inserts are dose forms that are solid or semisolid that do not have the drawbacks of conventional ophthalmic medication forms [5, 21]. Their vulnerability to defense mechanisms is lower. similar outflow through the nasolacrimal duct, have longer retention times in the conjunctival sac, and exhibit greater stability compared to traditional dose forms. Their undeniable benefits over traditional forms include precise dosing, the ability to minimize systemic absorption, and the potential for delayed drug release at a steady tempo. Additionally, by employing them, the frequency of therapeutic applications as well as the incidence of side effects and blurred vision can be decreased [8, 21]. For example, methylcellulose [22] and its derivatives, hydroxypropyl methylcellulose (HPMC) [8, 21–23], ethylcellulose [22, 24, 25], and polyvinylpyrrolidone are among the polymeric materials most frequently used in creating inserts. (PVP K-90) [8, 21, 25], polyvinyl alcohol [8, 23], gelatin [24, 26], chitosan [21] and its derivatives, such as carboxymethyl chitosan [22], and other combinations of the aforementioned polymers. The separation of inserts into soluble, insoluble, and biodegradable is indicated by the polymers used. An example of an insoluble insert using pilocarpine as an active component is the well-known Ocusert (Alza Corporation) insert, which is made from a copolymer of ethylene and vinyl acetate [5, 8, 27]. Patients' reluctance to give up conventional dose forms, their perception of a foreign object in their eyes, and occasional difficulties utilizing and introducing inserts—such as invisible excretion from the eye—remain the primary obstacles to the use of inserts in therapy [4, 5, 21, 27].

2.3.3. Drug Inserts for Ocular Solubility (SODI). Soluble eye inserts (SODI) are made of acrylamide, N-vinylpyrrolidone, and ethyl acrylate and come in the shape of tiny oval wafers. Tear fluid moisturises them once they are applied to the conjunctival sac, whereupon they soften and stick to the surface of the eye. This dose type was initially created so that astronauts may use it when they were weightless. SODI releases the drug in an irregular, pulsating fashion, and the dose form makes sure that the effect lasts a long time. Research on SODI has used neomycin, kanamycin, atropine, pilocarpine, dexamethasone, sulfapyridine, and tetracaine as active components [4, 28, 29].

2.3.4. OTS (Ocular Therapeutic System) minidiscs. Minidisc is a contact lens-like dosage form that is contoured, convex on the outside and concave on the side that comes into contact with the eye. lens diameter of 4-5 mm. Minidiscs are primarily made of two copolymers: poly(hydroxyethyl methacrylate) and α-τ-bis(4-methacryloxy)-butyl poly(dimethylsiloxane). The hydrophilic or hydrophobic nature of this dosage form allows for the prolonged release of both water-soluble and poorly water-soluble medications. Sulfisoxazole and gentamicin sulfate were two of the active substances used in minidisc research [2, 4, 28, 30].

2.3.5 Artificial Tear Inserts. This dosage form is made of hydroxypropyl cellulose and is a long, rod-shaped pellet without any preservatives. It is offered for sale. It is used to treat the dry eye syndrome under the brand name Lacrisert. Following its insertion into the conjunctival sac, the insert draws moisture from the cornea and conjunctiva to create a hydrophilic layer that hydrates and stabilizes the tear film [2, 5].

Collagen shield 2.3.6. Porcine sclera, whose collagen resembles that of the human cornea, is used to create collagen shields. Before being placed in the eye, the shields are moistened and kept in a dry state. When placed by an ophthalmologist, the typical collagen shields are not customized for each patient's ocular and can lead to certain discomfort as a result of eyesight interference. Furthermore, they could unintentionally be released from the eye shortly after insertion [5]. Collagen shields have been studied in both human and animal models. They may contain antiviral, antibacterial, or anti-inflammatory medications such as gentamicin. The use of collagen shields allowed for a larger medication concentration

to be obtained in the aqueous humor and cornea than was possible with contact lenses or eye drops [4, 30]. The so-called collasomes, which are tiny fragments of collagen (1 mm × 2 mm × 0.1 mm) suspended in a 1% methylcellulose medium, are more recent collagen dosage forms. Collasomes exhibit all the benefits of collagen shields without any drawbacks [5, 30].

2.3.7. The New Ocular Delivery System, or NODS. NODS is a patented dosage form held by Smith & Nephew Pharmaceuticals Ltd., which consists of a flag from The handle is connected to the active ingredient-containing polyvinyl alcohol by a soluble membrane. At the time of entry to the conjunctival sac, a drug-containing film splits from the handle and dissolves in the tear fluid, releasing the active ingredient. Compared to traditional eye drops, this approach guarantees the delivery of the prescribed medication dose to the eyeball and increases the active ingredient's bioavailability by up to eight times in the case of pilocarpine. Gamma radiation is used to sterilize NODS, which is devoid of preservatives.

2.3.8: Small tables. Minitablets are biodegradable, solid medication forms that transition into gels after being applied to the conjunctival sac, extending the duration of interaction between active substance and the surface of the eyeball, hence raising the bioavailability of the active ingredient. Minitablets have several benefits, such as being simple to apply to the conjunctival sac, resistant to defense mechanisms like tearing or outflow through the nasolacrimal duct, having mucoadhesive polymers that prolong contact with the cornea, and releasing the active ingredient from the formulation gradually at the application site due to the swelling of the outer carrier layers. The creation of minitablets that are inserted into the eye frequently calls for the use of polymers, or cellulose derivatives, such as sodium carboxymethyl cellulose, hydroxypropyl methylcellulose (HPMC), hydroxyethyl cellulose (HEC), and ethyl acrylates, or polyacrylic acid and its cross-linked derivatives, ethylcel cellulose, Carbopol, sometimes known as Carbomer, chitosan, starch—such as drum-dried waxy maize starch—and excipients—mannitol—which serve as lubricants, as well as sodium stearyl fumarate [35, 38] and magnesium stearate. Minitablets are created using either the direct compression method or the indirect method, which involves tableting the granules that were previously acquired. One benefit of the indirect method is the dry granulation step, which improves the flow characteristics of powders that frequently contain bioadhesive polymers. This allows for the creation of minitablets on a greater scale than that of a laboratory. Minitablets were produced using piroxicam, timolol, and other active components. acyclovir, ciprofloxacin, and gentamicin

2.4. Multicompartment Drug Delivery Systems

2.4.1. Micro- and Nanoparticles. The use of polymeric, solid, multicompartment drug delivery systems as ocular dosage forms shows promise. With courtesy Nanoparticles and microparticles can be differentiated in relation to the size of polymeric microvessels; the former range in size from 10 nm to 1000 nm, while the latter, when applied to the eyeball, range in size from 1 μm to 5–10 μm [4, 5, 8]. Polymeric carriers known as nanoparticles are composed of natural or synthetic polymers that are biodegradable, biocompatible, and frequently have mucoadhesive qualities. Sodium alginate, albumin, chitosan, poly(alkyl cyanoacrylate), polylactic acid, poly(epsilon-caprolactone), poly(lactic-co-glycolic acid), and gelatin were among the ingredients employed in its creation for application to the eyeball. These shapes can be separated into solid, monolithic spheres made of thick polymers called nanospheres. matrix, which contains the active component dispersed throughout, and nanocapsules, which are reservoirs made of polymer membranes enclosing the medication in either liquid or solid form. Diffusion or polymer degradation is the mechanism by which drugs are absorbed from nanospheres or nanocapsules after being applied to the conjunctival sac [8]. Journal of the Scientific World 5 When compared to typical eye drops, the active ingredient's bioavailability can be improved by employing nanoparticles as an ocular dosage form due to their larger dissolving surface and enhanced corneal penetration. However, the primary drawback of nanoparticles has been identified as their poor capacity [8]. The following medications have led to the development of nanoparticle delivery systems: sulfacetamide, levofloxacin, sparfloxacin, acyclovir, piroxicam, cyclosporine A, flurbiprofen,and pilocarpine.

2.4.2. The Liposome. Liposomes are phospholipid drug carriers that are typically composed of stearylamine, phosphatidylcholine, and varying concentrations of lecithin, cholesterol, and N-L-dipalmitoyl- Choline Phosphate [5]. The advantages of these carriers that have been highlighted include their relative intoxicity, biodegradability, biocompatibility, and amphiphilic qualities [4,5]. It is also highlighted that their stability is lower than that of therapeutic systems based on polymers [5, 8] and that the amount of space they have for containing drugs is constrained [8]. In addition, the large-scale production of them is highly technologically challenging and costly [8]. Their use in ocular medicine formulations enhances the administered substance's bioavailability and shields it from the enzymes found on the corneal epithelium's surface. It is important to note that efficacy Numerous parameters, including liposome size and charge, stability in conjunctival spaces, and encapsulation efficiency, affect how well liposomes distribute the active ingredient. affinity to the corneal surface, or val sac. Positively charged liposomes exhibit a greater affinity for negatively charged corneal surface and conjunctival mucoglycoproteins than do negatively and neutrally charged liposomes. As a result, they slow down the removal of the active ingredient from the application site. It has been suggested that liposome suspensions added to mucoadhesive gels or coated with mucoadhesive polymers promote the adhesion of negatively and neutrally charged liposomes to the corneal or conjunctival surface [4]. Liposomal ophthalmic medication formulations were being developed for the following active ingredients: acyclovir, pilocarpine, acetazolamide, chloramphenicol, and ciprofloxacin

2.4.3 The Niosome and the Discosome

Niosomes are twolayered carriers for both hydrophilic and hydrophobic particles that are chemically stable and made of nonionic surfactants. They lack the drawbacks of liposomes (phospholipid oxidative degradation, chemical instability, and high cost of natural phospholipids) [2, 5, 28]. Additionally, the duration of drug-to-cornea contact is prolonged by these biodegradable, biocompatible, and nonimmunogenic carriers, which raises the drug's bioavailability. Discosomes are altered niosomes that have the potential to transport eye medications. The range of their sizes is 12–16 μm. Discosomes are different from niosomes in that they have nonionic surfactants added to them. Solulan C24 is a lanolin derivative that is made of a combination of ethoxylated fatty alcohols and ether of cholesterol and polyethylene glycol.One of discosomes' advantages is their small, which keeps them out of the main circulation. Additionally, the disk shape guarantees that this form fits the conjunctival sac more snugly. Considerable investigation has already been carried out on niosomal medication formulations for drugs such as ganciclovir, cyclopentolate, or timolol.

2.4.4.Dendrimers

Dendrimers are three dimensional, branching, spherical, monodisperse polymer structures with a certain molecular mass, size, and shape. They might be utilized as carriers, which enclose the active component inside the polymer structure or form covalent or electrostatic interactions with the medication that is surface-bound due to the presence of several functional groups (carboxyl, hydroxyl, and amine). It has been demonstrated that polyamidoamine (PAMAM) dendrimers, which are utilized as ocular medication carriers, boost the bioavailability and prolong the duration of the active components' efficacy. Pupil-dilating tropicamide and pupil-constricting pilocarpine nitrate were the model substances used in studies on the use of dendrimers as ocular medication carriers. In this instance, the improved bioavailability of these compounds following application to the eyeball might be brought about by encapsulatinginside these structures, which causes the active substance to release slowly.Their bioadhesive qualities also provide an explanation.

2.5. Other Ophthalmic Drug Forms and Methods Of Application

2.5.1 Strips of filter paper. These are paper strips coated in pigments (such as fluorescein or Bengal Red) that are used to diagnose damage to the cornea, conjunctiva, or palpebrae.similar to identifying the existence of microbial infections and eye infections (such those caused by the Herpes simplex virus) [5]. Each 5 x 15 mm strip of the Fluorets preparation has

1 mg of sodium fluorescein in it. Typically, a drop of sterile saline solution is used to moisten the strip.

2.5.2. Mists. Seldom are sprays utilized as ocular medication formulations. They were created with cycloplegics, mydriatics, and their combinations as active components [5, Phenylephrine-tropicamide and Phenylephrine-tropicamide-cyclopentolate. The distance between the dose device and the eyeball should be between 5 and 10 cm prior to application. Using these forms has the benefit of allowing for the application of the medication on a closed eyelid, with an application that is roughly as effective as using eye drops made of the same chemicals. The miotic impact of pilocarpine hydrochloride sprayed directly onto the eyeball at concentrations of 1 to 4% for the active ingredient is nearly same, according to study by Martini and his colleagues.

2.5.3. Iontophoresis of the eye. It is a noninvasive process that uses direct current to deliver ions into tissues or cells. When use iontophoresis in pharmaceutical The previously described ions are really charged drug molecules; the anode introduces the positively charged molecule into the tissue, whereas the cathode introduces the negatively charged molecule. In most situations, iontophoresis yields a high drug concentration in the intended location while also facilitating quick, painless, and safe pharmaceutical application [5]. Gentamicin, dexamethasone, ciprofloxacin, and ketoconazole are among the active ingredients that were used in the research on introducing drugs using iontophoresis. It is important to note that administering antibiotics in this way increases their bactericidal activity [5].

III. EXAMINATIONS OF OPHTHALMIC DRUG FORMS PROPERTIES

There are two types of examinations that must be done to ascertain the properties: in vitro and in vivo. The former establish the pH, sterility, The factors that influence the quality of solutions include clarity, visual evaluation, particle size, viscosity, tonicity/osmolarity, amount of substance, amount of preservative, stability, and in vitro release [9, 13, 17, 26]. These latter consist of the in vivo release and the Draize eye test [13, 26]. Other noteworthy analyses, carried out for specific drug forms, include the measurement of encapsulation efficiency for multicompartment drug delivery systems and emulsions, or the analysis of ions and oxygen permeability for contact lenses [13, 17].

3.1. In Vitro Examinations

3.1.1. Analysis of Sterility. Sterility is a fundamental need for medication forms applied to the eye. As part of the sterility examination process, the aseptic conditions are inoculated with sample was grown on two types of microbiological media: soya-bean casein digest media, which contains casein and soy hydrolysate and is used to grow both aerobic and anaerobic bacteria, and thioglyco-late medium (fluid sodium mercaptoacetate or sodium thio-glycolate), which is used to grow both types of bacteria. A thioglycolate medium containing an applied sample is incubated at 30-35◦C, while a medium containing casein and soy hydrolysate and an applied sample is incubated at 20–25◦C for a maximum of 14 days. There are two distinct approaches for inoculating the sample under examination: direct vaccination as well as a technique utilizing membrane filters [9, 54, 55]. The direct injection technique outlined in Pharmacopoeia, which entails adding the appropriate volume of the inspected preparation to the medium. If a product contains antibacterial qualities, the substance's effects should be countered before the inspection. The ointments should be diluted with an appropriate sterile solvent containing the selected surface active ingredient prior to being introduced to the medium. The fluid containing the added samples should be checked at predetermined intervals throughout the incubation process [9, 55].

3.1.2: Calculating pH. The most common method for determining the pH of solutions, drops, suspensions, and in situ gels is the potentiometric method. Using this technique, the pH level is ascertained by measuring the potential difference between measurement (glass) electrode and reference (calomel or silver chloride) electrode, both placed in examined preparation, or between electrodes placed in examined and reference solutions of known pH. [9, 44, 48, 54–56]

3.1.3. Clarity Assessment. Examining formulation visually against a backdrop of white and black in appropriate lighting is known as a clarity examination. It is carried out for liquid forms, utilizing with the exception of prohibitions. Eye

drops and in situ gels both before and after gelling are covered by this investigation. Utilizing a UV-Vis spectrophotometer, trans-mittance testing is another technique for examining clarity. Research on contact lenses containing active substances can use this approach. The lenses are put on the surface of a quartz cuvette after being hydrated in physiological saline. After that, the transmittance is tested between 200 and 1000 nm in wavelength [17].

3.1.4. Analysis of Particle Size and Morphology. To examine the size of the particles, several techniques are used: optical microscopy (counting tiny particles), light electron microscopy (SEM, TEM, AFM), dynamic light scattering (DLS), Coulter Counter test, obscuration particle count test, dynamic image analysis, laser diffraction particle analyzers, and nanoparticle tracking analysis (NTA). The microscopic particle count test is an optical microscopy method. The American and International Pharmacopoeia requirements are included in the technique description. Samples are taken, rinsed, and dried on microporous membrane before being examined under a microscope.filter with holes that are no larger than 1 μm. The number of particles > 10 μm in the products under evaluation can be determined thanks to this examination. The test starts at a low magnification, like ×10 or ×50, where it is feasible to find larger than 25 micrometer particles. Next, at magnifications of ×100–×500, smaller particles are being looked for.[9]. The American Pharmacopoeia states that no more than 50 particles per milliliter (particle size ≥ 10 μm), no more than five particles per milliliter (particle size ≥ 25 μm), and no more than two particles per milliliter (particle size ≥ 50 μm) may be used in formulations. In contrast, the International Pharmacopoeia regulations provide that for every 10 μm of solid active component, a maximum of 20 particles must be larger than 25 μm, and no more than 2 of these particles may be larger than 50 μm. Not one of these constituents can be at least 90 μm in size at most. The examination of particles in difficult-to-filtrate, highly viscous liquids cannot be done using this method [9].

Test for Light Obscuration Particle Counting. A device that counts particles in liquid is used for the examination, and it uses a light obscuration sensor with an appropriat system dosing the sample to supply regulated sample portions for examination. Particles suspended in the liquid sample create variations in signal that are related to particle size as they float between the light source and the sensor. Air bubbles and drops of immiscible liquids are able to block enough light to be recorded alongside suspended particles due to the nature of the device that counts and identifies particles. By using the appropriate technique, these factors' influence on the measurement should be neutralized. There are several restrictions with this procedure for formulations that do not display viscosity and clarity near water. Additionally, compositions with color and high viscosity can show variations due to shear stress or goods containing bicarbonate buffer, for example, that cause air or gas bubbles to form at the instant of contact with the sensor also produce inaccurate readings. Membrane microscopy is the method used for measuring particle sizes in such formulations. When examining a formulation, the equipment used should have the maximum range of detected concentration (maximum number of particles per milliliter) greater than the predicted concentration of the formulation under examination. In addition, the equipment's dynamic range, or the range of particle sizes for which the amount and size can be precisely specified, must include the smallest size of particle that can be found in examined formulation.

Analysis of Dynamic Imaging. This analysis makes it possible to quantify the size and form of particles in suspensions or solutions. It entails capturing digital pictures of particles suspended in a flowing fluid, for instance, during mixing or flow, allowing for the specification of the particle size distribution and the marking of the quantity of particles in a certain volume. About 1 μm is the lower range of particle sizes that can be found using an optical microscope for dynamic imaging. With this technique, it is feasible to view particles throughout the whole size range of approximately 1 μm to more than 1000 μm. Nevertheless, seeing particles with sizes inside the entire range is not possible with a single measurement. It is not feasible to observe particles with sizes smaller than the lower range limit.Observe particles that are larger than the maximum range. Flow-based systems vary from one another in a number of ways, including the sampling strategy, digital picture quality, percentage of particles

analyzed simultaneously, and the concentration range at which measurements may be made. Particles stay suspended in the liquid during the real-time measurement, which is one of the primary benefits of the digital imaging method. It enables the imaging of extremely atypical particle forms and the observation of dynamic particle behavior in the presence of fluctuating size distribution.

Electron microscopy (TEM, AFM, SEM, and so forth). sophisticated microscopic techniques, including scanning electron microscopy (SEM) and transmission electron microscopy (TEM),and atomic force microscopy (AFM), which allow for high-quality, nanometer-resolution particle imaging. Nonetheless, robust sample processing is necessary for TEM and SEM. However, AFM makes it possible to capture the surface topology of the particles in the image with nanoscale accuracy. Due to the high cost of equipment, low efficiency, and variable sample examination conditions, all three methods are mostly suitable for specialized applications.

Dynamic Light Scattering (DLS) or Quasielastic Light Scattering, Photon Correlation Spectroscopy. The DLS technique monitors dispersed light variations brought on by Brownian Therefore has a connection to the diffusion coefficient and the movement of molecules in a solution. By utilizing the Stokes-Einstein equation and the diffusion coefficient value, one can ascertain the hydrodynamic particle radius within the sample under investigation. It is the sphere's radius when the particle being measured and its diffusion coefficient are equal. DLS makes it possible to quickly and easily quantify the size of particles for a single marking in the range of less than 1 nm to even 10 μm. can be carried out on active ingredient solutions or suspensions without formula dilution or modification for extremely tiny sample volumes (10–100 μL). DLS is the sole technique that allows for the wide range measurement of particle sizes in the solution, from approximately 0.3 to over 1000 nm, which helps to partially bridge the gap left by submicron analysis. Typically, this technique is applied in batch mode, using cuvettes or well plates to hold nonfractionated samples. Its drawbacks include its poor size resolution, inability to quantify shape, and tendency of small particles to disguise light scattering intensity in the presence of a significant number of bigger ones. Only when the hydrodynamic diameters of two distinct size groups diverge by two to five times does DLS resolve them [13]. Coulter Store. Using the principle that particles in an electric field alter the flow of charge (current), this technique works. Utilizing electrical means, the particle detector The sensing zone approach is applied. An ISO 13319 standard titled "Determination of particle size distribution—electrical sensing zone methods" describes how to use a Coulter Counter to measure the size and quantity of particles. By using this technology, the particles' sizes can be measured within the range of 0.4 μm to 1600 μm. Particles in the entire measurement range can be found thanks to a number of marks. This method's primary benefit is that the qualities of the particles—their color, shape, composition, or refractive index—don't impact the measurement. An extremely accurate distribution of particle sizes can be obtained with Coulter Counter. The measurement was preceded by a Particle-containing formulations need to be suspended in electrolyte, which could alter the amount or nature of the particles .

Analysis of Nanoparticle Tracking (NTA). A novel technique called NTA is used to measure particle sizes in the range of around 30 to 1000 nm. It combines dispersion of laser light with Particles in a solution can be seen and recorded by microscopy using a CCD camera. Similar to the DLS approach, the analysis uses the Stokes-Einstein equation to determine the particle's size. Compared to DLS, NTA displays a more precise size distribution; nevertheless, it necessitates a greater sample volume (about 300 μL).

3.1.5. Analysis of Substance or Preservative Content. The suitable analytical approach is indicated on the drug or preservative content examination in a given formulation. namely, HPLC or the spectrophotometric approach [12, 21, 26]. 3.1.6. Evaluation of Interaction/Compatibility between Drug and Carrier employing DSC, XRD, and FTIR techniques. In order to find possible interactions, tests using Fourier transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), and Xray diffractometry (XRD) are carried out for a variety of substances, including pure substances, physical mixtures of drugs and polymers used to

obtain formulation, and the formulation's ingredients.

Table 1: General conditions for stability examination [6].

Study	Storage condition	Minimum period coveredby data at submission
Long term*	25∘C ± 2∘C/60% RH1± 5% RH or 5% RH	12 Months
intermediate**	30∘C ± 2∘C/65% RH ± 5% RH	6 months
Accelerated	40∘C ± 2∘C/75% RH ± 5% RH	6 months

A Relative humidity

The applicant bears the responsibility of determining whether long-term stability studies are conducted at 25 ± 2 ∘C/60% RH ± 5% RH or 30 ± 2 ∘C/65% RH ± 5% RH. There is no intermediate condition if the long-term condition is 30°C ± 2°C/65% RH ± 5% RH.

between the preparation's other ingredients and the active ingredient [21].

3.1.7 Research on Drug Release. Several techniques used in the literature to assess the accessibility of medicinal substances in ocular forms were explained. These include the diffusion method using a Franz cell, the modified rotating paddle apparatus, the bottle method, the modified rotating basket method, and the flow-through device method. The bottle method. Using this procedure, the drug forms under examination are put into culture bottles [or vials [21] that contain artificial isotonic tear fluid or phosphate buffer at pH 7.4 [21]. Samples of the medium are often taken in designated conditions, and bottles and vials are typically shaken in water baths [21] (or incubated under magnetic stirring, primarily at a temperature of 37°C.time intervals and assessed with an appropriate analytical technique for drug quantity [21].

Diffusion Method with the Use of Franz Cell or Other Two- Compartment Systems. This technique uses a two-chamber system with a donor and a recipient compartment. A sample of the formulation under examination is put in a donor compartment of a Franz cell or other system, and a receiver compartment lds a thermostated dissolution medium that is continuously stirred with a magnetic stirrer, typically at a speed of 50 rpm. The temperature of the dissolution medium is 37 ∘C ± 0.5 ∘C. For example, a dialysis membrane made of cellophane separates the two chambers. Samples of the dissolving medium are taken during the examination at predetermined intervals, and the medicinal ingredient is labeled using an appropriate analytical technique.One possible glass container to utilize for the release testing in the approach outlined is a cylindrical glass container. It is put in a receiver compartment, or beaker. packed with either 7.4 pH phosphate buffer or artificial tear fluid. An examined drug form is placed in the cylindrical container that serves as the donor compartment. Next, a diffusion cell membrane is placed over the aperture of the container. Using a magnetic stirrer, the compartment's ingredients are continually mixed at a set temperature. Samples of the dissolving media are taken at predetermined intervals, and the medicinal material is identified using an appropriate analytical method. The amount of the taken sample is substituted with an equivalent amount of a brand-new solution.

Redesigned Rotating Paddle Device. Diffusion chambers, which are utilized in this procedure to analyze half-solid formulations, are put inside a paddle apparatus container. An appropriate liquid is added to the container and shaken at a test temperature of 37°C, for example, at a speed of 50 rpm. Dissolution medium-soaked diffusion chamber containers are submerged in water to maintain a temperature of 37 ± 0.5łC. At predetermined intervals, samples of the buffer solution containing the substance being released from diffusion chambers are obtained and their drug concentration is checked Flow-Through Equipment. This method uses a device for substance release investigations that allows for continuous dissolving medium circulation. The apparatus is composed of consisting of a water bath, a continuous duty oscillating pump, a jacketed flask holding a dissolution medium, and a jacketed

flow-through cell—the cell in which the chemical is dissolved. The jacketed flow-through cell is filled with a pharmacological form, and a dissolving solvent is added later. The medium has a closed cycle of circulation. The temperature is kept at a level that is similar to that of the human body (for example, 33 ± 2 C or 37 ∘ C). Samples are taken at predetermined intervals and their drug concentration is checked. Their drug concentration is checked.

It is possible to conduct examinations of the release of active components from drug forms in flow-through devices with open flow, as previously mentioned in papers by Rao and Tanwar and companions and Shyale. Additional tests carried out for ophthalmic drug forms include measurements of viscosity using viscometers, measurements of osmolarity using osmometers [44, 48, 56], and measurements of the light refractive index using ellipsometers/refractometers [20].

3.2. Other Examinations Performed for Chosen Drug Forms

3..2.1. Examinations for In Situ Gels

Analyzing Gel-Forming Capability. The purpose of this investigation is to evaluate the formulation's capacity to create gels on the surface of the eyeball. A selection of the scrutinized formulation is added to a vial containing a solution whose constituents mimic a tear fluid, and the sol-gel phase transition is evaluated using a visual method.

3.2.2. Examinations for Inserts

Swelling Measure. The degree of swelling exhibited by hydrophilic polymers varies based on the matrix network structure's relative resistance to the movement of water particles.. Low hydrogen bonding capacity polymer chains may not be able to establish a robust network structure that can withstand rapid water penetration. The rate at which water molecules diffuse into the hydrated matrix is directly proportional to the strength and number of hydrogen bonds that exist between polymer chains. The polymer must swell in order for its bioadhesive properties to begin to function, which happen shortly afterward. As polymer hydration increases, adhesion increases as well, until a point is reached where excessive hydration causes a sharp decline in adhesion strength due to the outer polymer layer untangling. The extent and velocityswelling and insert hydration both have an impact on the release of a medication from a dosage form. Consequently, this characteristic is most important for drugs. potential of bioadhesive matrix and release prediction. Bulk hydrophilicity and polymer hydration are measured using swelling investigation [21]. During the process, a certain number of inserts are selected, weighed, and placed individually in beakers holding a physiological saline buffered with phosphates solution [78], which mimics tear fluid [21] or pure water [85] at a set temperature, like 32°C ± 0.5°C [21]. Inserts are removed and dried within predetermined time frames. then weighed again after filter paper was added. The process is carried out again until mass expansion is no longer noticed [21]. The formula is used to determine the swelling index, or how much of the liquid is absorbed. The swelling index is calculated as [(w0 − w0)w0] × 100, (1), where w0 represents the starting sample weight and wt represents the sample weight at time t [21]. Investigations of Moisture Loss and Absorption. These tests are carried out to evaluate the physical stability and integrity of the polymer matrix of the inserts in dry and elevated moisture environments. [21]

. Investigations of Moisture Loss and Absorption. These tests are carried out to evaluate the physical stability and integrity of the polymer matrix of the inserts in dry circumstances and at increased wetness [21]. A certain quantity of inserts is selected and kept in a desiccator with a high moisture level—for instance, 75 ± 5% RH—for the purpose of examining moisture absorption. Inserts are removed and weighed once more after a predetermined amount of time, and the formula is used to determine the percentage of moisture absorption [21]. (Final weight - Initial weight) × 100 Initial weight = Moisture Absorption percentage

3.3. In Vivo Examinations

3.3.1. Eye Irritancy Test (Draize Eye Test). The Draize eye test (eye toxicity/irritancy test) is modified in numerous ways for different dose forms, such as solutions, emulsions, creams, solids—like inserts, for instance—and so on. Studies are typically conducted on rabbits, whose anatomy and physiology of the visual organs are extensively documented in the literature. Furthermore, compared to human eyes, rabbits' eyes are typically more sensitive to irritating

substances. Typically, three to six rabbits are utilized for the test, which addresses concerns about administering hazardous chemicals to small animals while still enabling the acquisition of dependable results. The most frequently employed animal subspecies are albino rabbits (from New Zealand, for example), which are weighed and examined.

prior to the test and subsequently housed in cages that have been specially made to prevent unintentional harm. The studied preparations are applied or injected into the conjunctival sac on the cornea itself. Initially, the eyeball was treated with roughly 0.1 mL of the substance under analysis. However, numerous follow-up tests suggested lowering this amount, for instance, to 0.01 mL, which more closely matches actual circumstances. One eye is utilized as a control in the test, typically the left one. The eyelids are typically remained closed for a short while after applying a medication form to the eyeball, though this is not necessary. On occasion, the eyeball surface is also rinsed with sterile liquids. Before and after the formulation is introduced, an evaluation of the state of the eyes is conducted. is carried out by seeing the eye in a proper light, frequently with the use of a slit lamp or magnifying lens to ensure a more accurate evaluation. Supplementary Techniques like fluorescein dyeing and capturing pictures of eyes make it easier to see changes. Furthermore, the quantity of blinks or rubbings of the eye following application may serve as an indicator of the degree of discomfort. Evaluations often occur one, two, four, and eight hours after administering a medication topically to the eye. If necessary, they may even occur seven or twenty-one days later. The length of the examination and its format are specifically tailored to the formulation under analysis. A scoring system is used to evaluate ocular changes, and each alteration in the cornea, conjunctiva, eyelid, or other and the iris is graded. Although other scoring systems have been offered in literature, the modified Friedenwald and Draize approaches are Currently in high demand [21] 3.3.2. Permeation of the Transcornea. Similar to the Draize eye test, transcorneal permeation studies involve selecting a sufficient number of healthy albino rabbits in order to get trustworthy outcomes. Following the introduction of the formulation to the conjunctival sac, the amount of active material in the aqueous humor is noted at predetermined intervals. A sample of aqueous humor is taken in the amount of approximately 150–200 μL using a syringe with needle after intramuscular or intravenous anaesthetic injection, which may contain, depending on application, ketamine hydrochloride, xylazine hydrochloride, or pento-barbital sodium. The sample is then stored at negative temperature, such as −20∘C, before HPLC analysis [13].

IV. CONCLUSIONS

The bulk of active ingredients used to treat ocular illnesses are still administered as eye drops, despite significant advancements in the field of ophthalmic dosage forms. A some of the most The pharmaceutical industry saw the introduction of complex forms, such as Alza Corporation's Ocusert, but researchers are still searching for the ideal ophthalmic system that would have controlled release, minimal systemic effects, ease of use, and prolonged retention time at the application site. Promising drug forms that can be mixed with other forms, including polymeric nanoparticles with the active ingredient suspended in the in situ gel, seem to be multicompartment systems. A challenge pertaining to the examination of their physicochemical characteristics and the correlation between in vitro and in vivo occurs in regard to the creation of novel ophthalmic dosage forms. emerges. This work reviews the body of research that makes it possible to arrange investigations on common and contemporary ophthalmic medication forms.

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