IJNRD.ORG ISSN : 2456-4184
INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD) | IJNRD.ORG
An International Open Access, Peer-reviewed, Refereed Journal

OPTHALMIC PREPARATIONS

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Abstract:

The Ophthalmic Preparation are Sterile Liquid, Semi-Solid, or Solid preparation intended for application to the Conjunctiva, the Conjunctival sac, or the eyelids. Topical dosage form constitute approximately 90% of the formulations to be available in market. Since a few yearsin the past until now, ophthalmic dosage paperwork elucidate essential demanding situations in scientific and pharmaceutical fields.

Keywords : Topical opthalmic drug forms, semisolid opthalmic dosage forms, solid opthalmic dosage forms, multi compartment drug delivery system, examinations of the drugs forms

Introduction:

Ophthalmic drug forms have been one of the most important and widely developed areas of pharmaceutical technology for dozens of years. The main reason of continuingly strong interest of scientists in these drug forms is the problem of a low bioavailability of medicinal substance after the application to the eyeball. It is caused by, amongst other reasons, the complicated anatomical structure of the eye, small absorptive surface and low transparency of the cornea, lipophilicity of corneal epithelium, metabolism, enzymolysis, bonding of the drug with proteins contained in tear fluid, and defence mechanisms, that is, tear formation, blinking, and flow of the substance through nasolacrimal duct . Low capacity of conjunctival sac, that is, approximately 30 μL without blinking, and the aforementioned defence mechanisms cause decrease in drug concentration in the place of application and shorten the time during which the active ingredient stays in the place of absorption.

Topical Ophthalmic Drug Forms:

1. Liquid Ophthalmic Drug Forms:

- **Eye Drops**:

Eye drops are accessible in the forms of water and oil solutions, emulsions, or suspensions of one or more active ingredients, which may contain preservatives if stored in multiuse packaging. These forms are sterile and isotonic. The optimum pH for eye drops equals that of tear fluid and is about 7.4. In deciding whether to buffer the drug in this form, one should take into account the stability of active ingredient and the tissue tolerance to the preparation. If the pH value gets outside the range of 4–8 which is tolerated by eye, the patient may feel discomfort, there may be irritation, and the drug bioavailability can decrease because of increased tearing.

- **Ophthalmic Solutions**:

Ophthalmic solutions are sterile, aqueous solutions used for, among other things, cleansing and rinsing eyeballs. They may contain excipients, which, for example, regulate osmotic pressure, the pH, and viscosity of the preparation. They may also contain preservatives if stored in multiuse packaging.

- **Microemulsions:**

Microemulsions are promising drug forms, inexpensive to produce, and easy to sterilize and stable, providing the possibility to introduce larger amounts of active ingredient. In vivo research and clinical examination of healthy volunteers proved extended time periods of effectiveness and increased bioavailability of drugs applied in these forms. The mechanism of action involves the adsorption of nanodrops constituting a reservoir of the drug and the inner phase of microemulsion on the corneal surface, which limits the overflow. Active ingredients for which microemulsions have been developed include difluprednate, cyclosporine A, flurbiprofen axetil, and the prodrug of flurbiprofen.

- **Modifications of Liquid Ophthalmic Dosage Forms**:

In the course of technological research on dosage forms, many ways have been proposed as to how to extend the time period of contact of liquid dosage forms with eye tissues, as well as to increase the active ingredient absorption to these tissues. These modifications include the addition of substances which increase viscosity, introducing the drug penetration enhancing substances to formulation, using prodrugs or cyclodextrins.

- **Addition of Substances Increasing Viscosity/Adhesion**:

Extending the time period of contact with cornea and improving bioavailability of substances may be obtained by increasing formulation's viscosity. Substances which have such effect include hydrophilic polymers of high molecular weight which do not diffuse through biological membranes and which form three-dimensional networks in the water. Examples of such polymers include polyvinyl alcohol, poloxamers, hyaluronic acid, carbomers, and polysaccharides, that is, cellulose derivatives, gellan gum, and xanthan gum. The aforementioned carbomer is used in liquid and semisolid formulations as a suspending substance or a substance which increases viscosity, whereas hyaluronic acid is used as a polymer, forming biodegradable and biocompatible matrix, which enables extending time periods of drug release.

- **Addition of Penetration Increasing Substances**:

The purpose of using penetration increasing substances in ophthalmic drugs is to enhance their corneal absorption by modifying the continuity of corneal epithelium structure. Research has shown that such properties are displayed by chelating agents, preservatives (like benzalkonium chloride), surfactants, and bile acid salts. However, these substances displayed local toxicity, which caused restrictions in their use in ophthalmic (drug forms technology. The Scientific World Journal 3

- **Prodrugs:**

Modifying drug properties by developing prodrugs also enables increasing drug permeability through the cornea. This method involves modification of chemical structure, which gives the active ingredient new properties, that is, selectivity and site specificity. Examples of medicinal substances for which prodrugs were developed include epinephrine, phenylephrine, timolol, and pilocarpine. Dipivefrine, a diester of pivalic acid and epinephrine, displays seventeenfold higher permeability through the cornea than epinephrine, which is caused by its six hundredfold higher lipophilicity at pH 7.2. Therefore, a smaller dose of dipivefrine applied over the eyeball has similar therapeutic effect to epinephrine. In comparison to conventional eye drops containing 2% epinephrine, eye drops with dipivefrine 0.1% display only slightly smaller activity lowering the intraocular pressure with significant reduction of side effects.

- **Cyclodextrins:**

Cyclodextrins are cyclic oligosaccharides able to form inclusion complexes with active ingredients, thus increasing the solubility in water of hydrophobic compounds without changing their molecular structure. As carriers, they enable keeping hydrophobic drugs in solution and transport them to biomembranes surface. In the case of ophthalmic drugs, optimal bioava(<15%) in aqueous eye drops solution. The most often used cyclodextrin in developing forms applied over the eyeball is 2-hydroxypropyl-β-cyclodextrin, which does not show irritating effects. Eye drops containing drug inclusion complexes, namely, dexamethasone or pilocarpine with 2-hydroxypropyl-β-cyclodextrin, are well tolerated and ensure increased bioavailability in comparison to conventional ones.

2.Semisolid Ophthalmic Drug Forms :

- **In Situ Gels (or Sol-to-Gel Systems):**

In situ gels are viscous liquids, showing the ability to undergo sol-to-gel transitions when influenced by external factors, like appropriate pH, temperature, and the presence of electrolytes. This property causes slowing of drug drainage from the eyeball surface and increase of the active ingredient bioavailability. Polymers employed in developing these drug forms include gellan gum, poloxamer, and cellulose acetate phthalate, whereas active ingredients used in the course of research on in situ gels include ciprofloxacin hydrochloride, timolol maleate, fluconazole, ganciclovir, and pilocarpine.

- **Eye Ointments:**

Ointments are semisolid dosage forms for external use, usually consisting of solid or semisolid hydrocarbon base of melting or softening point close to human body temperature. After applying the ointment to the eye, it decomposes into small drops, which stay for a longer time period in conjunctival sac, thus increasing drug's bioavailability. Eye ointments have certain disadvantages— although they are well tolerated and safe, they cause, among other things, blurring of vision and sometimes have irritating effects, because of which they are mainly applied nighttime.

3. Solid Ophthalmic Drug Forms :

- **Contact Lenses Coated with Drugs:**

This drug form can absorb on its surface water-soluble substances, released after applying the drug over the eyeball for a longer period of time. The first and most widely used polymer in the production of lenses was the cross-linked poly(2-hydroxyethyl methacrylate) with small amount of ethylene glycol dimethylacrylate. In recent years, research has been conducted on employing silicon-based lenses. Interest in contact lenses still grows, which is confirmed by increase in the number of articles on its use published in recent years. Examples of drugs whose pharmaceutical availability from lenses was researched include timolol, ciprofloxacin, dexamethasone, and cyclosporine.

- **Ocular Inserts:**

Inserts are solid or semisolid dosage forms without disadvantages of traditional ophthalmic drug forms.They are less susceptible to defence mechanisms like outflow through nasolacrimal duct, show the ability to stay in conjunctival sac for a longer period, and are more stable than conventional dosage forms. Their undoubtable advantages over conventional forms are also accurate dosing, the possibility of slow substance release with constant speed, and limiting its systemic absorption.Polymeric materials most often employed in developing inserts include, for example, methylcellulose and its derivatives, that is, hydroxypropyl methylcellulose (HPMC) , ethylcellulose, polyvinylpyrrolidone (PVP K-90), polyvinyl alcohol, chitosan and its derivatives, like carboxymethyl chitosan, gelatin, and various mixtures of the aforementioned polymers.

- **SODI (Soluble Ophthalmic Drug Inserts):**

SODI are soluble eye inserts in the form of small oval wafers, produced from acrylamide, *N*-vinylpyrrolidone, and ethyl acrylate. After their application to conjunctival sac, they are moistened by tear fluid, and then they soften and adhere to eyeball surface. This dosage form was originally developed for astronauts to apply it in the state of weightlessness. Drug is released from SODI in a pulsational, uncontrolled manner, and the dosage form ensures its prolonged effect. Active ingredients employed in the course of research on 4 The Scientific World Journal SODI include neomycin, kanamycin, atropine, pilocarpine, dexamethasone, sulfapyridine, and tetracaine.

- **Minidiscs/OTS (Ocular Therapeutic System):**

Minidisc is a profiled, convex outside, concave from the side of contact with eye surface, dosage form similar to a contact lens with 4-5 mm diameter. Main copolymers from which minidiscs are developed are *α*-*ω*-bis(4-methacryloxy)-butyl poly(dimethylsiloxane) and poly(hydroxyethyl methacrylate). This dosage form may be either hydrophilic or hydrophobic, which enables extended time period of release of water-soluble and poorly water-soluble drugs. Active ingredients employed in research on minidiscs were, among others, sulfisoxazole and gentamicin sulfate.

- **Artificial Tear Inserts**:

This dosage form is a long, rodshaped pellet, containing no preservatives and developed from hydroxypropyl cellulose. It is available on the market under the name Lacrisert and is employed in treatment of the dry eye syndrome. After its introduction to conjunctival sac, the insert absorbs water from conjunctiva and cornea, forming a hydrophilic layer, which stabilizes the tear film and moistens the cornea.

- **Collagen Shield:**

Collagen shields are developed from porcine sclera, whose collagen displays similarities to the one in human cornea. The shields are stored in dry state and hydrated before they are introduced to the eye. The standard collagen shields, applied by an ophthalmologist, are not individually suited to the patient's eyeball and cause certain discomfort due to interfering with vision. Moreover, they may be accidentally excreted from the eye just after introduction. Collagen shields were tested on animal and human models and may be carriers of antibiotics like gentamicin, antiinflammatory drugs like dexamethasone or antiviral drugs. In comparison to contact lenses and eye drops, the use of collagen shields enabled obtaining higher drug concentration in the cornea and the aqueous humor. More recent dosage forms built from collagen are the so-called collasomes, small pieces of collagen (1 mm × 2 mm × 0.1 mm) suspended in a 1% methylcellulose vehicle. Collasomes show all advantages of collagen shields without disadvantages of the latter.

- **NODS (New Ophthalmic Delivery System)**:

NODS is a dosage form patented by Smith and Nephew Pharmaceuticals Ltd, consisting of solidified paper handle and a flag from polyvinyl alcohol, containing the active ingredient, attached to the handle with a soluble membrane. A film containing drug separates from the handle at the point of introduction to conjunctival sac and dissolves in the tear fluid, releasing the active ingredient. This system ensures delivery of specified drug dose to the eyeball and increased bioavailability of active ingredient (even eightfold in the case of pilocarpine) in comparison to conventional eye drops. NODS does not contain preservatives and is sterilized with gamma rays .

- **Minitablets:**

Minitablets are biodegradable, solid drug forms, that, after application to conjunctival sac, transit into gels, which extends the time period of contact between active ingredient and the eyeball surface, which in turn increases the active ingredient's bioavailability. The advantages of minitablets include easy application to conjunctival sac, resistance to defence mechanisms like tearing or outflow through nasolacrimal duct, longer contact with the cornea caused by presence of mucoadhesive polymers, and gradual release of active ingredient from the formulation in

the place of application due to the swelling of the outer carrier layers. The development of minitablets applied to the eyeball usually involves using polymers, that is, cellulose derivatives, like hydroxypropyl methylcellulose (HPMC), hydroxyethyl cellulose (HEC), sodium carboxymethyl cellulose, ethyl cellulose, acrylates, that is, polyacrylic acid and its cross-linked forms, Carbopol or Carbomer, chitosan, starch, for example, drum-dried waxy maize starch, and excipients, that is, mannitol, performing the function of solubilizate or sodium stearyl fumarate and magnesium stearate with lubricating properties.

4. Multicompartment Drug Delivery Systems :

- **Nanoparticles and Microparticles:**

Polymeric, solid, multicompartment drug delivery systems are promising dosage forms for application to the eyeball. With respect to the size of polymeric microvessels, nanoparticles and microparticles can be distinguished, the former's size being from 10 nm to 1000 nm and the latter's, in case of application to the eyeball, from 1 μm to 5–10 μm. Nanoparticles are polymeric carriers, built from biodegradable, biocompatible, natural, or synthetic polymers with often mucoadhesive properties. Ingredients used in its development, for the purpose of application to the eyeball, were poly(alkyl cyanoacrylate), polylactic acid, poly(epsilon-caprolactone), poly(lactic-co-glycolic acid), chitosan, gelatin, sodium alginate, and albumin.

- **Liposomes:**

Liposomes are phospholipid drug carriers usually built of phosphatidylcholine, stearylamine, and various amounts of cholesterol or lecithin and α-L-dipalmitoylphosphatidylcholine. The pointed-out advantages of these carriers are their biocompatibility, biodegradability, amphiphilic properties, and relative intoxicity. However, it is also emphasized that their stability is smaller in comparison to therapeutic systems based on polymers and that their volume in which drug can be contained is limited.Moreover, their large-scale production is expensive and very difficult technologically.Their employment in ophthalmic drug forms enables improvement of bioavailability of applied substance and its protection from enzymes present on the surface of corneal epithelium.It should be emphasized that effectiveness in delivery of the active ingredient from liposomes depends on many factors, that is, encapsulation efficiency, size and charge of liposomes, stability of liposomes in conjunctival sac, or affinity to corneal surface.

- **Niosomes and Discosomes:**

Niosomes are chemically stable, built of nonionic surfactants, two-layered carriers used for both hydrophilic and hydrophobic particles, without the disadvantages of liposomes (chemical instability, oxidative degradation of phospholipids, and expensiveness of natural phospholipids). Moreover, these biodegradable, biocompatible, and nonimmunogenic carriers extend the time period of contact between drug and cornea, which in turn increases drug's bioavailability. Discosomes are modified forms of niosomes, which also may act as carriers for ophthalmic drugs. Their size varies from 12 to 16 μm. Discosomes differ from niosomes in that the former contain the addition of nonionic surfactants, Solulan C24, a derivative of lanolin, which is a mixture of ethoxylated cholesterol (ether of cholesterol and polyethylene glycol) and ethoxylated fatty alcohols (ether of cetyl alcohol and polyethylene glycol). The size of discosomes is their advantage, because of which they do not enter the general circulation.

- **Dendrimers:**

Dendrimers are branched, spherical, monodisperse, three-dimensional polymer structures, of specific size, shape, and molecular mass. They may be used as carriers, which enclose the active ingredient inside the polymer structure or create, due to the presence of many functional groups (carboxyl, hydroxyl, and amine), electrostatic or covalence bonds with the surface-bound drug . It has been proved that polyamidoamine (PAMAM) dendrimers, used as carriers for ophthalmic drugs, extend the duration of active ingredients' effectiveness and increase their bioavailability. Research on using dendrimers as ophthalmic drug carriers was conducted for model substances: the pupil dilating tropicamide and pupil constricting pilocarpine nitrate. The increased bioavailability of these

substances after application to the eyeball may be in this case caused by enclosing the drug inside these structures, which results in slower release of the active ingredient. It is also explained by their bioadhesive properties.

5. Other Ophthalmic Drug Forms and Methods of Application:

- **Filter Paper Strips:**

These are paper strips covered with pigments (i.e., fluorescein or Bengal Red) and used in diagnostics of corneal, conjunctival, or palpebral damage, as well as in diagnosing the presence of microbiological infections and eyeball infection (for example with Herpes simplex virus). Every strip of the Fluorets preparation, sized approximately 5×15 mm, contains 1 mg of sodium fluorescein. The strip is usually wetted with a drop of sterile saline solution.

- **Sprays:**

Sprays are rarely used ophthalmic dosage forms. Active ingredients for which they were developed include cycloplegics, mydriatics, and their mixtures, that is, phenylephrine-tropicamide and phenylephrinetropicamide-cyclopentolate. Before application to the eye, the distance between dosage device and the eyeball should range from 5 to 10 cm. Results of research conducted by Martini and his associates proved that miotic effect of pilocarpine hydrochloride applied to the eyeball in the form of spray with the active ingredient concentration at 1 to 4% is close to the effect achieved after applying eye drops of 1% concentration, with the volume of dose applied in spray being 5 μL, which was 6 times lower than one applied in eye drops.

- **Ocular Iontophoresis**:

It is a noninvasive procedure during which ions are introduced to cells or tissues by use of direct current. When iontophoresis is used in pharmacotherapy, the aforementioned ions are charged drug molecules, with positively charged molecule being introduced to tissue from anode and the negatively charged one from cathode. Iontophoresis enables fast, safe, and painless pharmacotherapy and in most cases also obtains high drug concentration in the desired area. Active ingredients that were employed in the course of research on introducing drug using iontophoresis include gentamicin, dexamethasone, ciprofloxacin, and ketoconazole, and it is emphasized that applying antibiotics using this method enhances their bactericidal activity.

6.Examinations of Ophthalmic Drug Forms Properties Examinations :

These have to be performed in order to determine the properties may be divided into performed in vitro and in vivo. The former determine sterility, the pH, clarity of solutions, visual assessment, size of the particles, tonicity/osmolarity, viscosity, amount of substance, amount of preservative, stability, and in vitro release. The latter include the Draize eye test and the in vivo release. Other distinguished examinations, performed for chosen drug forms, include analysis of ions and oxygen permeability for contact lenses or determination of encapsulation efficiency for multicompartment drug delivery systems and emulsions.

- ***In Vitro* Examinations** :
- **Sterility 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.

- **Determining pH:**

The pH of solutions, drops, suspensions, and in situ gels is most often determined using a potentiometric method. In this method, the pH value is determined by measuring potential difference between electrodes placed in examined and reference solutions of known pH or between measurement (glass) electrode and reference (calomel or silver chloride) electrode, both placed in examined preparation.

- **Clarity Examination:**

Clarity examination involves the visual assessment of formulation in suitable lighting on white and black background. It is performed for liquid forms, with the exception of suspensions. This examination applies to eye drops and in situ gels before and after gelling. Another method of clarity examination involves transmittance measurement using a UV-Vis spectrophotometer. This method can be employed in research on contact lenses filled with active ingredients. The lenses are hydrated in physiological saline and placed on the surface of quartz cuvette. The transmittance is measured afterwards from 200 to 1000 nm wavelength.

- **Examination of Size and Morphology of Particles:**

For examination of particles' size multiple methods are employed: optical microscopy (microscopic particle count test), light obscuration particle count test, dynamic imaging analysis, laser diffraction particle analyzers, electron microscopy (SEM, TEM, AFM), DLS (dynamic light scattering), Coulter Counter test, and nanoparticle tracking analysis (NTA). Optical Microscopy Method (Microscopic Particle Count Test). Description of this method includes requirements from both American and International Pharmacopoeia. The examination is performed under microscope after taking sample, rinsing, and drying it on microporous membrane 7 filter with pores' diameter ≤ 1 μm. related to the concentration of particles—as it grows, the required sample volume falls. DLS (Dynamic Light Scattering) or Photon Correlation Spectroscopy, Quasielastic Light Scattering.

- **Examination of Content of Substance or Preservative:**

The examination of drug or preservative content in given formulation is labeled with relevant analytical technique, that is, spectrophotometric method or HPLC.

- **Examination of Drug and Carrier Interaction/Compatibility Using FTIR, DSC, and XRD Methods:**

Fourier transform infrared spectroscopy (FTIR) and examinations employing differential scanning calorimetry (DSC) and Xray diffractometry (XRD) are performed for, among others, pure substance, physical mixtures of drug and polymers used to obtain formulation, and the ingredients of the formulation in order to identify potential interactions between the active ingredient and other ingredients of the preparation.

- **Stability Examination:**

The purpose of stability examination is to provide information on changes in quality of active ingredient or medicinal product in time due to the effect of environmental factors, that is, temperature, humidity, and light, on examined substance/product, as well as to set the date of further examination of medicinal substance or expiry date of medicinal product and recommended storage conditions. General stability requirements for ophthalmic products, for example, drops and ointments, are similar to those for other pharmaceutical products. They are harmonized through ICH (International Conference on Harmonisation) process in USA, Europe, and Japan, acknowledging the contribution of a European institution EMEA (European Agency for the Evaluation of Medicinal Products) and its Committee for Proprietary Medicinal Products (CPMP), QWP (Quality Working Party), and the American institution FDA (Food and Drug Administration) as well as the Japanese Ministry of Health. .

➢ **Drug Release Studies:**

In literature, several methods employed for the examination of accessibility of pharmaceutical substance from ophthalmic forms were described. They include bottle method, modified rotating basket method, diffusion method with the use of Franz cell, modified rotating paddle apparatus, or method with the use of flow-through device. Bottle Method. In this method, the examined drug forms are placed in culture bottles or vials containing phosphate buffer at pH 7.4 or artificial isotonic tear fluid . Bottles and vials are usually shaken in water baths (or incubated under magnetic stirring, mostly at a temperature of 37◦ C, and the medium samples are taken in specified time intervals and examined for drug amount using a suitable analytical method. Diffusion Method with the Use of Franz Cell or Other TwoCompartment Systems. This method employs a two-chamber system consisting of two compartments: donor and receiver.

Other Examinations Performed for Chosen Drug Forms:

➢ **Examinations for In Situ Gels Examination of Gel-Forming Ability**:

This examination is performed in order to assess the ability of formulation to form gels on the surface of eyeball. A sample of examined formulation is introduced to a vial containing a solution whose components simulate a tear fluid and visual technique is employed to assess the sol-gel phase transition .

➢ **Examinations for Inserts Swelling Index:**

Hydrophilic polymers of different structures exhibit different swelling degree, depending on relative resistance of matrix network structure to water particles' movement. Polymer chains exhibiting low ability to form hydrogen bonds may not be able to form strong network structure, resistant to fast water penetration. Swelling of the polymer is vital to activation of bioadhesive abilities, which activate just after swelling begins. In specified time intervals, inserts are taken out, dried with filter paper, and weighed once more. The procedure is repeated until the moment when mass growth is not observed anymore. The degree to which the liquid is taken up, called the swelling index, is calculated from the formula.

$$\textbf{Swelling index} = [(Wt - W0)/\ W0\ ] \times 100,$$

where $W0$ is the initial sample weight and Wt is the sample weight at t time

➢ **Examinations for Multicompartment Drug Delivery Systems Encapsulation Efficiency:**

A sample for encapsulation efficiency examination is obtained by centrifuging or centrifugal ultrafiltration of mixture formed after preparing the formulation. The obtained supernatant or filtrate is examined for amount of free active substance using a spectrophotometric method or HPLC. Encapsulation efficiency is calculated from the formula

$$\textbf{E.E.(\%)} = (W\textbf{total} - W\textbf{free}) \times 100/\ W\textbf{total}\ ,$$

where Wtotal is the total amount of drug in the formulation; Wfree is the amount of drug in the filtrate/supernatant.

❖ ***In Vivo* Examinations:**

➢ **Eye Irritancy Test (Draize Eye Test):**

There are many modifications of eye toxicity/irritancy test (Draize eye test) performed for dosage forms, that is, solutions, emulsions, ointments, solids, for example, inserts, and so forth. Examinations are usually carried out on rabbits, whose vision organ anatomy and physiology are well described in literature. Moreover, rabbits' eyes are usually more susceptible to irritating compounds than those of humans. For the test, usually from 3 to 6 rabbits are used, which, on one hand, enables obtaining reliable results, and, on the other hand, is an answer to claims for applying toxic substances to as little animals as possible. The most often used animal subspecies are albino (e.g., New Zealand) rabbits, which are examined and weighed The Scientific World Journal 11 before the test and then

placed in specifically adapted cages, designed so as to avoid accidental injuries. The examined preparations are introduced to conjunctival sac or applied directly on the cornea.

- **Transcorneal Permeation Study:**

For transcorneal permeation study, as in the Draize eye test, healthy albino rabbits are chosen in the number which is suitable for obtaining reliable results. The amount of active substance in aqueous humor after introducing the formulation to conjunctival sac is marked in specified time intervals. Using a syringe with needle, after intramuscular or intravenous anaesthetic injection which may contain, depending on application, ketamine hydrochloride, xylazine hydrochloride, or pentobarbital sodium, a sample of aqueous humor is taken in the amount of about 150–200 μL and stored at negative temperature, for example, −20◦ C, before HPLC analysis. At times, additional inhalation anaesthesia is used, for example, in the form of mixture of 4% isofluraneoxygen, shortly before or during paracentesis. Regional anaesthesia, for example, in the form of xylocaine solution, may also be applied. Noomwong with associates, during performed tests, added suitable amount of 2% ZnSO4 ·

- ***In Vivo* Release Evaluation of Inserts:**

For in vivo release evaluation, formulations which gave desired results in in vitro release evaluations are chosen. Inserts are put in conjunctival sacs of healthy rabbits chosen for studies. In specified time intervals, inserts are carefully taken out and examined for left drug amount using a suitable analytic technique.

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. 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.

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