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Novel Techniques in the Opthalmic Drug Delivery System

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ABSTRACT

In order to effectively treat eye conditions, the drug must be concentrated at the eye for an adequate amount of time. The barriers defending the eye hinder ocular medication delivery. The biggest challenge is frequently overcoming the active drug substance's bioavailability. The goal of this review was to concentrate on novel techniques in the ophthalmic drug delivery system. The ultimate result will be improved yields, reduced bioavailability problems, higher productivity, and less downtime.

INTRODUCTION:

Opthalmic preparations are specialized dosage forms designed to be instilled onto external surface of the eye(topical) administered inside(intraocular) or adjacent(periocular) to the eye or used in conjugation with an ophthalmic device. One of the most intriguing and difficult tasks facing pharmaceutical scientists is ophthalmic drug delivery. The eye's physiology, biochemistry, and anatomy make it a unique organ extremely resistant to foreign chemicals. Conventional methods for treating vision-threatening ocular illnesses, such as eye drops, suspensions, and ointments, cannot be regarded as ideal. However, eye drops make for more than 90% of the commercially available ophthalmic formulations.

To treat ocular disorders more effectively and with fewer side effects, a number of innovative drug delivery technologies are now in development. The majority of these technologies attempt to sustain medication release for extended periods of time. This would lower the total frequency of administration and the requirement for doctor visits in the case of intravitreal injections, greatly lowering treatment expenses and raising the standard of living for patients with eye disorders.

- Ideal Characteristics of Opthalmic Drug Delivery System:

1. It needs to be sterile.

2. To body fluids, it needs to be isotonic.

3. pH and buffer adjustment.

4. Less of a tendency to drain.

5. Minimum binding of proteins.

- Advantages of Opthalmic Drug Delivery System:

1. It can be administered with ease.

2. They have a quick impact and absorption.

3. Fewer systemic and external consequences.

4. Better patient compliance.

- Disadvantages of Opthalmic Drug Delivery System:

1. At the eye surface, the residence time of the drug is less.

2. Poor bioavailability.

3. The instability of the dissolved drug.

4. After the bottle is opened, the shelf life is shorter due to the reduced concentration of preservatives.

- Novel Drug Delivery System:

It is the evolution of an existing drug molecule from a conventional form which significantly improves its performance in terms of patient compliance, safety and efficacy.

The following are the main goals of the Novel Approach:

1. To circumvent the protective barriers of the eye without causing permanent tissue damage.

2. To provide sustained and controlled drug delivery.

3. To improve the bioavailability by increasing the corneal contact time of the drug.

4. To minimize the side effects produced by conventional systems.

CONVENTIONAL OPTHALMIC DRUG DELIVERY SYSTEM:

- Liquids:

1) Solutions: Ophthalmic solutions are sterile aqueous liquids that are instilled into the eye. In accordance with the label instructions, this dosage includes solid preparations which can be reconstituted into solutions. Increasing the viscosity of the ophthalmic solutions upto 20 centipoise (cP) can increase the corneal contact time.

2) Suspensions: The dosage forms contain an aqueous solvent with an appropriate suspending agent and dispersing agent that is used to disperse finely divided insoluble Active

Pharmaceutical Ingredient. By using ophthalmic solutions, a drug substance's time in contact with the cornea can be extended, resulting in a more prolonged action.

3) Emulsions: The drug's low aqueous solubility is the reason for creating an ophthalmic solution. In order to create a uniform oil-in-water emulsion, ophthalmic emulsions are made by dissolving or dispersing the active ingredient(s) into an oil phase, adding the appropriate emulsifying and suspending agents, and vigorously mixing with water.

4) Powders for Reconstitution: Drugs that have a limited shelf life in liquid form are prepared as sterile powders and given to the pharmacist for reconstitution before being given to the patient.

5) Sol to Gel Systems: Solutions that can be instilled as eye drops because they are liquid in the container, but gel when they come into touch with the tear film. This prolonged contact time may improve drug absorption and lengthen the duration of the therapeutic action.

- Semi-Solids:

1) Ointments: These are mixtures of paraffins, which have a melting point of 34°C at eye temperature and are both semisolid and solid hydrocarbons. Ointments quickly melt when applied to the inferior conjunctival sac, and any leftover product runs over the lid margin, lashes, and skin of the lids. It has a therapeutic effect of 6hrs.

2) Gels: Mucoadhesive polymers are used in ophthalmic gels to deliver an active ingredient to the eye in a targeted manner. Bioadhesion, which refers to the attachment of a drug carrier to a particular biological tissue, is a feature of mucoadhesive polymers. The lengthened duration the drug spends in contact with the biological tissue increases the bioavailability of the drug to the eye. The selection of polymer has a significant impact on the drug's release kinetics from the dosage form. Sodium alginate, carboxymethylcellulose, carbopol, and polycarbophil are a few examples of polymers used in ophthalmic gels.

- Solids:

1) Ocular Inserts: Ophthalmic inserts and ocular systems are solid dosage forms that are applied to the cornea, lachrymal punctum, or conjunctival fornix. Inserts come in two varieties: erodible (soluble) and nonerodible (insoluble). These devices improve ocular bioavailability while providing precise dose distribution. Because they are solid dosage

forms, ocular inserts can be used instead of more conventional ophthalmic systems like aqueous solutions, suspensions, and ointments.

2) Contact Lenses: When contact lenses are soaked in drug solutions, they can absorb drugs that are water-soluble. In order to release the drug over an extended period of time, these contact lenses are drug-saturated. It is possible to extend the drug's ocular residence period by using hydrophilic contact lenses. In humans, the Bionite lens is usually used for drug delivery.

- Intraocular Dosage Form:

1) Implants: In the ocular fluid and posterior segment tissue, Implants provide an extended-release of the drug, whereas different polymer concentrations can change the rate of delivery. Biodegradable and non-biodegradable implants are the two categories of implants based on how quickly they degrade.

2) Irritating Solutions: A balanced salt solution was prepared for the cornea's hydration and clarity during surgery. It contains the five necessary ions: chloride, sodium, potassium, calcium, and magnesium. A potential source of bicarbonate is also present, along with acetate ions.

3) Injections: To achieve larger therapeutic concentrations intraocularly than are typically possible with topical or systemic administration, the ophthalmologist delivers anti-infectives, corticosteroids, and anesthetic products using available parenteral dosage forms.

NOVEL CONCEPTS OF OPTHALMIC DRUG DELIVERY SYSTEM:

- Microemulsion:

These are small droplet sizes (about 100 nm) and have a transparent appearance due to high level of dispersion of the internal phase. They are thermodynamically stable systems consisting of a dispersion of water and oil by a combination of surfactant and co-surfactant to reduce interfacial tension. The inner phase of the microemulsion on the corneal surface, which limits the overflow, and the adsorption of nano drops, which serve as a drug reservoir, are the key components of the mechanism of action.

Microemulsions have been prepared for the active ingredients like difluprednate, cyclosporine A, flurbiprofen axetil, and flurbiprofen prodrug.

Marketed formulation sold as Pyrimon-DF (Combination of Moxifloxacin and Difluprednate) is an example of the Microemulsion preparation.

- Nanosuspension:

Nanosuspensions are colloidal systems made up of sub-micron-sized, poorly soluble drugs suspended in a surfactant-stabilized dispersion medium. Typically, polymeric resins in nanosuspensions increase the drug's solubility and, as a result, improve bioavailability. These resins are inert in nature. Nanosuspensions are composed of several biodegradable or non-biodegradable polymers, lipids, phospholipids, or metals and are non-irritating. They also carry a charge that aids in their attachment to the cornea. They can be divided into two categories: Nanospheres (in which the drug has been evenly spread) and Nanocapsules (where the drug has been coated within the polymeric material).

- Liposomes:

Liposomes are phospholipid drug delivery systems that are typically made of phosphatidylcholine, stearyl amine, and varying concentrations of lecithin, -L-dipalmitoyl-phosphatidylcholine, and cholesterol. These liposomes have great biocompatibility, natural phospholipids, and cell-like membranes, making them potential vehicles for delivering ocular drugs. It has drawbacks such a low drug load and poor aqueous stability. Acyclovir, pilocarpine, acetazolamide, chloramphenicol, and ciprofloxacin are among the active ingredients for which liposomal ophthalmic medication formulations were being developed.

- Niosomes:

Niosomes are nonionic bilayered structural vesicles with the capacity to encapsulate both hydrophilic and lipophilic substances. Niosomes enhance residence time and decrease systemic drainage, which increases ocular bioavailability. Niosomes have been developed because they are more chemically stable than liposomes, which allows them to overcome the constraints of liposomes, such as their chemical instability, oxidative phospholipid degradation, cost, and lack of purity in natural phospholipids.

- Discosomes:

The inclusion of nonionic surfactants, such as Solulan C24, a lanolin derivative made of ethoxylated cholesterol (a combination of cholesterol and polyethylene glycol), and ethoxylated fatty alcohols makes discosomes different from niosomes (ether of cetyl alcohol and polyethylene glycol). The benefit of discosomes' size is that it prevents them from entering the bloodstream.

- Dendrimers:

Dendrimers are macromolecular molecules with branching polymers that trap hydrophilic and lipophilic medications in the central core. The choice of functional group on the surface (amine, carboxylate, and hydroxyl), size, and molecular weight of the dendrimer are a few of the crucial factors for building a delivery system.

- Hydrogels:

Three-dimensional, hydrophilic polymeric networks called hydrogels are able to absorb huge volumes of water or biological fluids. Hydrogel formulation can significantly enhance residence time. In a case study, the determination of anti-inflammatory potential of aspirin was studied on the carrageenan-induced rabbit eye model and the presence of the hydrogel matrix-forming polymer sustained the drug release and corneal permeation for more than 6 hours.

- Iontophoresis:

Due to its noninvasive distribution to both the anterior and posterior segment, Ocular Iontophoresis has recently attracted a lot of interest. Ionized medications can be transferred through membranes with minimal electrical current using the non-invasive technique of Iontophoresis. Two methods, migration and electro-osmosis, are used to transport the medicines through the membranes. Gentamicin, dexamethasone, ciprofloxacin, and ketoconazole were among the active ingredients used in studies on the introduction of drugs using Iontophoresis.

- Ultrasound:

A unique drug delivery method called ultrasound drug delivery involves applying ultrasound waves (20 kHz for 1 hour) over the cornea to deliver the medicine. The cornea's permeability is considerably increased by ultrasound. Examples of ultrasound drug delivery include the administration of beta-blockers such as atenolol and timolol for the treatment of glaucoma.

EVALUATION OF OPHTHALMIC PRODUCTS:

The following tests are used to evaluate ophthalmic preparations: -

- Test for Sterility:

The absence of a viable microbial infection is referred to as sterility. Each and every ophthalmic formulation must be sterile. If Pseudomonas aeruginosa is present, contaminated ophthalmic formulations may potentially result in eye infections that eventually result in blindness. As a result, ophthalmic formulations must be made using aseptic methods in a laminar flow hood, just as intravenous formulations. Sterile containers must be used to package the sterile compositions. According to USP and BP, the sterility test can be carried out either by using the membrane filtering method or by directly contaminating the culture media with the product being tested.

➢ Direct Inoculation of The Culture Medium: Transfer the specified amount of the preparation to be tested into the culture medium in accordance with BP so that the product's quantity never exceeds 10% of the medium's volume unless otherwise directed. If the product being tested exhibits antibacterial action, conduct the test after neutralising it with a suitable neutralizer or by diluting it sufficiently in culture media. It may be best to use a concentrated culture medium set up in a way that accounts for the subsequent dilution when it is necessary to apply a large amount of the product. The concentrated medium is frequently added to the product in its container when necessary.

➢ Membrane Filtration: When the nature of the product permits, such as for filterable aqueous preparations, alcoholic or oily preparations, and preparations miscible with or soluble in aqueous or oily solvents provided the solvents do not have an antimicrobial impact in the test conditions, the method of membrane filtration is used. The method outlined here implies that membranes with a diameter of about 50 mm can be employed. The quantities of

the dilutions and subsequently the washings must be appropriately adjusted if filters with a specific width are employed. The filtering device and membrane have undergone sterilization. The apparatus is only intended to enable aseptic transport and filtering of the solution under examination; it also allows aseptic membrane removal for medium transfer.

- Presence of Metal Particles:

This examination is only required for ophthalmic ointments. The corneal or conjunctival surface of the eye will itch if there are metal particles present.

Ten ointment tubes are used in the procedure. Each tube's contents are thoroughly transferred to a petri dish with a clean, flat bottom measuring 60 mm in diameter.

• The product is heated for two hours at 85 degrees Celsius with the lid closed. The item is melted, evenly distributed, and then cooled to room temperature.

• After the cover has solidified, remove it. After that, a 30x optical microscope is used to study the bottom surface.

• A 45-degree top external light source has been used to illuminate the viewing surface. A calibrated ocular micrometre is used to count the number of particles 50mm or larger on the bottom surface of the ointment.

• According to the USP, there should be no more than 50 of these particles in a set of 10 tubes, with no more than 8 particles each tube.

- Test for Clarity

There must be no extraneous materials in ophthalmic preparations. Visual inspection in the proper lighting is used to carry this out, as well as the use of tools like light scattering or video image projection.

• Visual inspection: the preparation is examined in proper lighting, shielded from reflection into the eyes, and viewed against a black-and-white background with content that is in motion with a swirling activity.

• Instrumental method: This method destroys product units while gaining information about particle count and size distribution through the use of electric resistance, light scattering, and

light absorption. Without damaging the product units utilized for inline detection, an instrumental technique using video image projection may detect moving particles.

- Test for Leakage

This inspection is performed on an ophthalmic ointment to see whether the tube and seal are still intact. The outer surfaces of 10 sealed containers are chosen, and they are cleaned.

• In an oven that has been preheated to 60 degrees for eight hours, they are placed horizontally over absorbent blotting paper. If there is no leakage from any tube, the test is considered successful. If there is leakage, the test is repeated with an additional 20 tubes. If there are no more than 1 leaky tube out of 30 in the test, it is successful.

CONCLUSION:

Ophthalmic dosage forms have a very wide application and have been developed as a promising treatment in terms of ocular diseases. The unique ability to provide physical stability, sustained, and site-specific drug delivery for a scheduled period of time can open new vistas for precise, safe, and effective treatment in the current scientific landscape, where the area of novel drug delivery systems has been recognised for its tangible benefits. Non-conventional approaches such as microemulsions, nanosuspensions, niosomes, liposomes, discosomes, hydrogels, dendrimers, ultrasound, and iontophoresis not only reduce the repeated administration to overcome non-compliance but also helps to increase the therapeutic value by reducing toxicity and increasing bioavailability and so on.

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