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NOVEL OCULAR DRUG DELIVERY SYSTEM

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ABSTRACT

The major barrier faced by today's pharmacologists and formulation scientists is ocular drug delivery. The topical eye drop is the most convenient route of drug administration, especially for the treatment of anterior segment diseases. On the other hand, for posterior ocular delivery, research has been immensely focused on the development of drug-releasing devices and nanoformulations for treating chronic vitreoretinal diseases. These novel devices or formulations may help to surpass ocular problems and associated side effects with conventional topical drops.

KEYWORDS

Ocular inserts, Osmosis, Biopolymeric, Cubosomes, Spanlastics and Hyalugel.

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INTRODUCTION

The eye is a complex organ with unique anatomy and physiology. The structure of the eye can be divided into two main parts: The anterior segment and the posterior segment. The anterior segment of the eye occupies approximately one-third while the remaining portion is occupied by the posterior segment. Tissues such as the cornea, conjunctiva, aqueous humor, iris, ciliary body, and lens make up the anterior portion. The back of the eye or posterior segment of the eye includes sclera, choroid, retinal pigment epithelium, neural retina, optic nerve and vitreous humor. Conventional systems like eye drops, suspensions and ointments cannot be considered optimal in the treatment of vision-threatening ocular diseases[1]. However, more than 90% of the marketed ophthalmic formulations are in

the form of eye drops. These formulations mainly target the anterior segment of eye diseases[2].

IONTOPHORESIS

Iontophoresis is a tool for delivering a high concentration of an ionized drug into the anterior and posterior eye using low-intensity electric current William James Mortan and Stephen Ledue during mid 18 century, the investigated the drug delivery by applying electric current termed iontophoresis[3].

Mechanism of Iontophoretic drug delivery

Ionic drug transportation into eyes through electro repulsion and electro-osmotic flow, these depend on flux enhancement of ions.

Electro-repulsion - Mild electric field produced between cathode electrodes for negatively charged drug or anode electrode for positively charged drug results in accumulation of the drug in the vitreous segment and aqueous segment of eye through sclera and cornea.

Electro-osmotic flow - Electrical force of charged ions (drug) flows across a semipermeable membrane due to a down concentration gradient.

Both mechanisms follow passive diffusion[3].

Approaches to ocular iontophoresis

Trans-corneal iontophoresis is the attainment of maximum concentration of drug in the anterior portion of an eye by passing through the corneal membrane for treatment of glaucoma, corneal ulcer and eye inflammation.

E.g.:

Enhancement of Gentamicin permeationso, antibioticis administered as an effective way to treat bacterial keratitis and ocular infection.

Trans-scleral iontophoresis is the attainment of maximum and sustained drug concentration (prolonged release) in the vitreoretinal or posterior segment of the eye for treating uveitis and other disorder that occur in blindness[4].

Devices

Widely used ionotropic devices are EYEGATE®-II delivery, OCUPHORE® delivery, and VISULEXTM

The Eye Gate II iontophoresis drug delivery system relies on electric current to pull an ionizable drug into the eye. It is done by placing an electrode on the forehead of the patient and the opposite electrode is placed along with the drug-carrying applicator. As the ionized drug liquid is dispensed into the eye, a small amount of current is produced between the electrodes, helping the drug to completely absorb into the eye[3].

OCULAR INSERTS

Ocular inserts are defined as sterile, thin, multi-layered, drug-impregnated, solid, or semisolid consistency devices placed into the cul-de-sac or conjunctival sac, whose size and shape are specially designed for ophthalmic application. Its main objective is to increase the contact time between the drug and conjunctival tissue to ensure sustained release for topical system treatment[5].

The mechanism of controlled drug release into the eye is as follows:

Diffusion, B. Osmosis, C. Bio-erosion[6].

Diffusion

In the Diffusion process, the drug is continuously released at a limited rate through the cellular membrane into the tear fluid. If the insert is formed of a solid non-erodible body with pores and dispersed drug. The release of the drug can take place via diffusion through the pores. A controlled release can be regulated by the gradual dissolution of solid drugs within the matrix as a result of inward diffusion of aqueous solutions. In a solubilized device, true dissolution occurs mainly through polymer swelling. In swelling-controlled devices, the active agent is homogeneously dispersed in a glassy polymer. Due to the glassy nature of the polymer, no diffusion occurs through the dry matrix. When the insert is placed in the eye, water from the tear fluid begins to penetrate the matrix, then swelling and consequently, polymer chain relaxation and drug diffusion take place. The dissolution of the matrix, which follows the swelling process, depends on polymer structure: linear amorphous polymers dissolve much faster than cross linked or partially crystalline polymers[6].

Osmosis

In the Osmosis process, the insert comprises a transverse impermeable elastic membrane dividing the interior portion of an insert into a first compartment and a second compartment

The first compartment is bounded by a semi-permeable membrane and the impermeable elastic membrane, and the second compartment is bounded by an impermeable material and the elastic membrane. There is a drug release aperture in the impermeable wall of the insert[6].

The first compartment contains a solute that will not pass through the semi-permeable membrane and the second compartment contains a reservoir for the drug which is in liquid or gel form. When the insert is produced in the aqueous environment of the eye, the aqueous layer diffuses through the first compartment and stretches the elastic membrane to expand the first compartment and in the second compartment, the drug is forced through the drug release aperture[6,7].

Bioerosion

In the Bioerosion mechanism, the configuration of the body of the insert is constituted from a matrix of bio-erodible material in which the drug is dispersed. Contact of insert filled with tear fluid results in controlled sustained release of the drug through the matrix by bioerosion method. The drug may be dispersed uniformly throughout the matrix but it is believed a more controlled release is obtained if the drug is superficially concentrated in the matrix. In truly erodible or E-type devices, the rate of drug release is controlled by a chemical or enzymatic hydrolytic reaction that leads to polymer solubilization, or degradation to smaller, water-soluble molecules. These polymers, as specified by Heller 34 may undergo bulk or surface hydrolysis. Erodible inserts undergoing surface hydrolysis can produce zero orderkinetics; provided that all devices maintained a constant surface geometry and the drug is poorly water-soluble[6,7].

Classification of ophthalmic inserts

Based upon their solubility behaviour[7,8,9].

Insoluble

a) Diffusion b) Osmotic and c) Contact lens

Soluble

a) Based on natural polymers e.g. Collagen

b) Based on synthetic or semi-synthetic polymers e.g., cellulose derivatives like HPMC, HPC, MC etc[7,8,9]

CONTACT LENSES

Precision1 lenses feature Smart Surface Technology, a permanent micro-thin high-performance layer of moisture that steps up from 51% water at the core to greater than 80% water at the outer surface. Alcon says that a single 6-o'clock scribe mark makes fitting the lens easy[10,11].

Therapeutic contact lenses (TCLs) were often used in the management of corneal and ocular surface diseases (OSDs)[10,11].

Contact lenses are shaped structures and are initially used for vision correction. Their use has been extended as potential drug delivery devices by pre-soaking them in drug solutions. The main advantage of this system is the possibility of correcting vision and releasing drugs simultaneously. It is further subdivided into 5 groups.

Rigid

Semi-rigid

Elastomeric

Soft hydrophilic

Bio-polymeric

The therapeutic application of contact lenses is an essential element in ophthalmic care. Materials that are used currently include polymethyl methacrylate (PMMA), cellulose acetate butyrate, siloxane-containing polymethacrylates, silicones and hydrogels. Suitable material used in a contact lens is determined by its physical, chemical, and mechanical properties. Fabrication techniques are also important, affecting lens diameter and base curve. Selection and fitting of contact lenses require knowledge of how different contact lenses affect corneal physiology and results of therapeutic lens use in selected clinical situations (including recurrent erosion, meta herpetic ulcers, and other epithelial defects[11,12,13].

CYCLODEXTRINS

Cyclodextrin comes under the family of cyclic glucopyranose oligosaccharides. It is composed of 6-8 glucose units that form water-soluble inclusion of complexes with many poorly soluble lipophilic drugs. So CDs are used to improve the aqueous solubility and BA of highly hydrophobic drugs. CD and CD complexes possess similar biological properties but different physicochemical properties. These oligosaccharides are non-toxic in nature and pharmacologically inactive excipients for both drug and food products. Cyclodextrin and CD complexes form nanoparticles that self-assemble to form microparticles under certain conditions[13].

Nabih Maria *et al* incorporated curcumin with β - cyclodextrin and hydroxypropyl- β- cyclodextrin in about two molar ratios of 1:1 and 1:2 using the co-solvent to improve the poor aqueous solubility and low stability of curcumin[13]. It is done by the process of sonication of co-solvent and freeze-drying methods. The formulations were characterized by then characterized using differential scanning calorimetry, Fourier transforms IR spectroscopy, SEM techniques, solubility assessment, powder X-ray diffraction studies, and in vitro release studies. Among these methods, the freeze-drying method produces highly water-soluble drug-CD complexes[14]. The stability studies affirm that pH 6.8 phosphate buffer containing 1% Tween 80 was selected as the release medium for in vitro release studies because curcumin is highly stable in this medium. Among the 12 formulations, the F11 formulation can sustain the release of the drug for more than 96 hours with a maximum amount of released drug (21.77±0.26μg/ml). The curcumin cyclodextrin. Inclusion complex follows Higuchi non-Fickian diffusion mechanism for *in-vitro* release of the drug. Hence f11 is formulated as an eye drop which is used as a sustained release delivery system for the treatment of retinitis pigmentosa[13].

The major limitation of CDs is that the availability of administration routes is limited and supergeneric strategies were not getting success.

The most commonly researched CD is 2-hydroxy propyl beta-cyclodextrin as an ocular delivery[13].

Drugs used along with HPBCD

Disulfiram shows enhanced BA of the drug across the corneal membrane when it is used as an eye drop formulation

Along with HPMC the eye drop formulation shows successful suppression of the cataract effect

Ketoconazole shows enhanced BA of drugs in aqueous humor and cornea

Indomethacin shows delayed release and a high drug stability effect[13].

CUBOSOMES

Cubosomes are liquid crystalline particles whose size ranges between 100-300nm. They are formulated by dispersion of liquid crystalline cubic aggregates in aqueous media and they are characterized by higher surface area and similar structure to their parent cubic aggregates. They are prepared by using amphiphilic lipids molecules such as glycerol monooleate (GMO) and phytantriol which can self-assemble in water to form cubic structures which involve curved bicontinuous lipid bilayers which look similar to 3d honeycombed (cavernous) arrangement[14].

Preparation

There are two main approaches for cubosomes preparation, the top-down and bottom-up approaches[14],

Top-down approach

In the top down-method, the cubosomes form lipid mixed with a suitable stabilizer such as F127 to form the bulk viscous cubic aggregates. These aggregates are dispersed in aqueous media by the application of high energy. The advantage of this method is that the aggregates are meant to be stable for up to a year. The disadvantage of this method is that it requires a higher amount of energy input in large-scale production which may also cause a problem when temperature-sensitive molecules such as peptides are used[14].

Bottom-down method

This method involves the cubosomes forming lipid, the stabilizer F127 and a hydro trope are dispersed

in aqueous media with the application of lower energy. The hydro trope is a molecule that can dissolve water-insoluble lipids to form lipid precursors and prevent the occurrence of liquid crystals. It can solubilize molecules that can solubilize poorly soluble agents in presence of aqueous media by hydrotropic solubilization. Urea, sodium alginate, and sodium benzoate are most commonly used as hydro topes. The advantages of this method are that it requires minimal energy input and it can be used for the preparation of temperature-sensitive molecules[14].

Application of cubosomes in ODDS

Since the cubosomes are biodegradable, they can encapsulate molecules such as hydrophilic, hydrophobic, and amphiphilic with high loading efficiency and render bioactive agents with the targeted release.

It improves ocular BA of the encapsulated drugs because of the long residence time on the cornea and is characterized by mucoadhesive properties due to the presence of GMO.

Cubosomes loaded with dexamethasone show an increase in the apparent permeability coefficient and an increase in the dexamethasone concentration in aqueous humor. It also significantly increases the preocular retention time compared to Dex-Na phosphate eye drops.

Tropicamide shows a faster onset of action and higher intensity of mydriatic actions when incorporated with cubosomes[14].

Drawbacks

Because of the higher viscosity of the cubic phase it is very hard to prepare in large-scale production.

Because of the higher water content inside their structure, it shows low encapsulated efficiency for water-soluble drug molecules[14].

Advantages

Cubosomes can envelop hydrophilic, hydrophobic, and amphiphilic drug molecules with it.

Enhances the BA of poorly-water soluble drugs.

Simple techniques

It can protect the drug molecule from the effect of physical and chemical degradation.

Larger amounts of the drug can be incorporated due to their high internal surface[14].

SPANLASTICS

Spanlastics are surfactant-based nano vesicular system that contains non-ionic surfactant and spans (sorbitan esters) which entraps the drug into the core in the form of the bilayer. As the name suggests spanlastics (Span + Elastic) are span-containing formulations that are highly deformable and elastic carriers.

They are amphiphilic in nature, in which the drug molecules are encapsulated in a vesicle of a non-ionic surfactant. It can entrap the molecule, osmotically active and stable. They are more flexible in their structural characteristic so they can be easily modulated. It protects the encapsulated drug molecules from a biological environment[15].

Spanlastics are a special type of nano vesicular system which are more deformable and multilamellar in comparison to niosomes. It can overcome the disadvantages associated with liposomes such as chemical instability.

Spanlastics contain edge activators (tween) which reduce the interfacial tension between vesicles and also help by improving the fluidity and deformability of the spanlastics.

It acts as a site-specific drug delivery system for targeting drugs to the targeted sites such as ocular, oral, topical, nasal and trans ungual applications[15,16].

Advantages

Spanlastics are biodegradable and non-immunogenic in nature.

It enhances the BA of the drug molecule because the drug molecule has shielded from the effect of the environment.

They are less toxic in nature and highly compatible due to the presence of non-ionic surfactants in their structure.

Because of their high elasticity and deformability in nature they can easily squeeze through the cornea and reaches the anterior segment of an eye as well as the posterior segment of the eye to target the

retinal pigment epithelium, vitreous cavity, and choroid.

The non-ionic surfactant-based spanlastics are non-irritant to the eyes[15,16].

Classification of Spanlastics

Multi-Lamellar Vesicles (MLV)

Large Unilamellar Vesicles (LUV)

Small Unilamellar Vesicles (SUV)

Methods used in the preparation

Sonication

Hand shaking method

Ether injection method

Extrusion method

Micro fluidization method

Shilpa Kakkar *et al* developed a spanlastics using ketoconazole which has a molecular weight of 531.44 Daltons and a limiting solubility of 0.04 mg/ml which shows a poor penetration across the cornea in the normal formulation. The spanlastics were elastic in nature and showed 2 times better corneal permeation ($p \leq 0.001$). It was safe in terms of genotoxicity, cytotoxicity and in OECD guidelines.

Nano range spanlastics are promising nanocarriers for selective delivery of the posterior part even though the drug has low permeability and solubility profile. The various class of drugs like anti-HIV, anti-angiogenesis, anti-vascular, etc can be formulated as spanlastics[15,16].

NANOEMULSIONS

Nanoemulsions are small, spherical, submicron-sized colloidal particulate system which is used as carriers of drug molecules. Its sizes range vary from 10 to 1,000nm. Its surface consists of amorphous and lipophilic with a negative charge. Nanoemulsions are thermodynamically stable isotropic systems in which water and oil are combined to form a single phaseby adding amphiphilic surfactants or mix with a droplet diameter of size ranging from 0.5 to 100 micrometers.

In ophthalmic formulation, the protection of the epithelial layers in the eyes lead to poor bioavailability of drug molecule. Nano-size range drug provides high penetration into the deeper layer of tissues so nanoemulsions are developed as colloidal O/W or W/O nanodispersions and homogenous systems with surfactants to reduce the interfacial tension between the two phases. In nanoemulsion, the droplet size will be <150nm[17,18].

Types

Oil in water type of nanoemulsion

Water in oil type of nanoemulsion

Advantages

Nano emulsions enhance the BA of the drug molecule.

It is non-toxic and non-irritantin nature hence it is comfortably used in as ocular formulations.

It contains minute droplets having a greater surface area which in turn provides greater absorption.

Nanoemulsions tend to be formulated as foams, creams, liquids, and sprays.

It tends to solubilize the lipophilic drug molecule[18,19].

Disadvantages

Surfactants which is used in the formulation should be devoid of toxic substances.

Expensive process

Components of nanoemulsion

Water

Oil phase (olive oil, castoroil, oleic acid, and isopropyl myristate)

Surfactant (Tween 20, 80; span 20, Labrasol)

Co-surfactant (propylene glycol, PEG 200,400)

The surfactant is used for the reduction of interfacial tension between the two phases.

The co-surfactant is used along with the surface for enhancement of the stability of nanoemulsion[18,19].

Method of preparation

High energy method: it includes three methods namely high-pressurehomogenizer; ultrasonication and micro fluidization

High-pressure homogenizer method which includes the preparation of the nanoemulsion occurs by inducing high-pressure homogenization by a high-pressure homogenizer or piston homogenizer. By this method, we can produce an O/W type of nanoemulsion of < 20% oil phase and extremely

minute particles that are less than 1nm can be prepared.

Ultrasonication method is used in the case of coarse emulsion which can be converted into nano-sized particles by influencing the ultrasonic field.

Micro fluidization method implies high pressured pump of 50020000PSI which produces very fine sub-micron range particles are produced.

Low energy method: it includes phase inversion method and spontaneous nano-emulsification method

Phase inversion method is based on the intense changes in physical properties such as particle size, the temperature which is developed to covert O/W to W/O type of nano-emulsion

In the spontaneous nano-emulsification method, the preparation of homogeneous organic solutions is carried out which is then transferred into the aqueous phase by continuous stirring using a magnetic stirrer which produces an o/w type of nano-emulsion. Water miscible solvents are then removed by the evaporation process[19].

Instability problems in nanoemulsion

Flocculation
Creaming
Cracking
Phase inversion

Evaluation of nano-emulsion

The nanoemulsion can be evaluated by the following
Droplet size analysis
Viscosity determination
Dilution test
Drug content
Polydispersity
Dye test
Refractive index determination
Zeta potential determination
Fluorescence test
Percentage transmittance
Conductance measurement
Filter paper test[18,19]

OCULAR MICROEMULSIONS

Micro-emulsions are colloidal nano dispersion systems whose size range present between 5-200nm. The microemulsion has significant thermodynamic stability and low surface tension which results in enhanced drug absorption. Microemulsion enhances the retention time of ocular drug absorption. MEs are generally easy to apply as compared to conventional eye solutions. It contains benefits like less frequent instillation, betterretaining and prolonged drug action. Drugs like antibiotics, anti-fungal, anti-inflammatory, and immune suppressive drugs can be impregnated into a microemulsion[20].

MEs are used especially for poorly water-solubledrugs. The microemulsion was mainly composed of four different phases such as oil phase, aqueousphase, surfactant, and co-surfactant.

Types of microemulsion

W/O type of micro-emulsion
O/W type of micro-emulsion
Bi-continuous micro-emulsion
Liquid crystalline micro-emulsion

Formulation

Oil phase (such as ethyl oleate, octanoicacid, oleic acid, and isopropyl palmitate)
Aqueous phase (such as water)
Surfactant (such as soya phosphatidylcholine; tween 20, 80; span
20, 80; sodium cholate; lecithin; and polyglycerol fatty acid esters) *co-surfactant (such as ethanol, propanol, propan 1, 2-diol, PEG, and glycerol)[20,21].

Preparation of Micro-emulsions

Microemulsions are prepared by one of these methods
Phase inversion method
Phase titration method

The phase titration method is commonly used which is done by the spontaneous diffusion of solvent or surfactants into the continuous phase due to ultra-low interfacial tension[20]

Advantages

It can deliver both hydrophilic and hydrophobic drug molecules effectively to the ocular tissues.

It is more suitable for topical ophthalmic application because of eyedrop-like consistency, smaller particle size, and phase transition behavior.
Because of the phase transition it can form in-situ precorneal depots which helps in the prolonged release of the drug.
It exhibits better physicochemical properties and stability.
MEs can deliver the drug to both the anterior and posterior parts of the eye[19,22].

Drawbacks

The nanoparticles are stabilized only by inducing larger concentrations of the surfactants and co-surfactants.
MEs stability can be altered by pH and temperature[20].

Application

Ocular MEs are used in the treatment of various conditions such as
Glaucoma
Anti-inflammatory ocular conditions
Against fungal infection[20]

COMBINED STRATEGIES

To a polymer matrix, the incorporation of the drugs nanocarrier results in a system that has the advantages of nanocarrier and gel formulations[22].

ADVANTAGES

Easy administrations with good tolerance
Prevention of enzymatic metabolism that presents in the tear film and protects the drug from this metabolism
Prolonged retention time
Sustained release
Enhanced BA and enhanced drug penetration in the anterior and posterior parts of the eyes
The commonly used polymer are alginates, chitosan, cellulose derivatives, poloxamer, hyaluronic acid, and carbomer[22,20].

HYALUGEL INTEGRATED LIPOSOME

Hyalugel integrated liposome is one of the novel ODDS which is prepared by integrating the hyaluronic acid (HA) inside the liposome vesicles. Inspire of the advantages of liposomes in ODDS, they also contain some drawbacks such as poor stability, early drug leakage, and short residence time. So liposomal structure has been modified by combining with a hydrogel which helps to reduce these drawbacks. Hyaluronic acids are natural substances that are found in the fluid of the eyes. Among the other hydrogels, Hyaluronic acid hydrogel is considered a bio-compatible, biodegradable, and non-toxic polymer. Other than these benefits, HA has the potential to act as a mucoadhesive polymer and as a depot system to increase drug localisation. HA is used in the treatment of dry eye syndrome, and ocular fungal infections[23].

PREPARATION

Hyalugel-integrated liposomes are prepared by a simple lipid film hydration technique. Lipoid S10, cholesterol, and drug were dissolved in the mixture of chloroform and methanol in a 250ml round bottom flask. Then evaporation is done by using a Rotary evaporator for 1.5 hours after the formation of drug residue (to remove solvent completely). Then these drug residue films are hydrated using HA in different concentrations with a hydration time of 1 hour.
Hyalugel-integrated liposome enhances corneal permeability and prolongs the residence time. This formulation reduces the frequency of administration (i.e., the administration once a day in place of 3-4times/day). Thus, it increases patient compliance[23].

IN-SITU GELLING ODDS

The in-situ gelling ophthalmic drug delivery system consists of polymer which changes their structure due to environmental factors like pH, temperature, and ionic strength. The in-situ forming gel is in liquid form during instillation to the eye then in response to environmental changes turns liquid to viscoelastic gel in a cul-de-sac of the eye. Release of the drug slowly in a sustained manner with extended residence time lead to enhancing the bioavailability, minimising systemic absorption, and

reducing the frequency of dosage regimen which improves patient compliance[24,25].

MECHANISM OF GELLING SYSTEM

Temperature triggered in-situ gel system is based on using temperature-sensitive polymers like cellulose derivatives, chitosan, xyloglucan, and poloxamers. Below low critical solution temperature (LCST) system in the liquid form; above LCST, the gel formed at pre-corneal temperature (35 degrees Celsius)

pH triggered in-situ gel system is based on pH-sensitive polymers like polyacrylic acid (Carbopol 940), polycarbophil and cellulose acetate phthalate (CAP) contains acidic or basic groups which accept or release protons. Hence, alterations in pH take place i.e., pH 4.4 as solution form; pH 7.4 as gel form in tear fluid.

Ion-activated in-situ gel system; is based on using ion-activated polymers like gellan gum, hyaluronic acid, sodium alginate, and pectin. They interact with cations (Na+, ca+) present in tear fluid which produces gel to extend the corneal contact time

Nanocarriers in-situ gelling system; Nanosuspension and lipid-based nanocarriers are the most effective formulation of in-situ gelling systems, thus increasing bioavailability and pre-corneal residence time.

Example

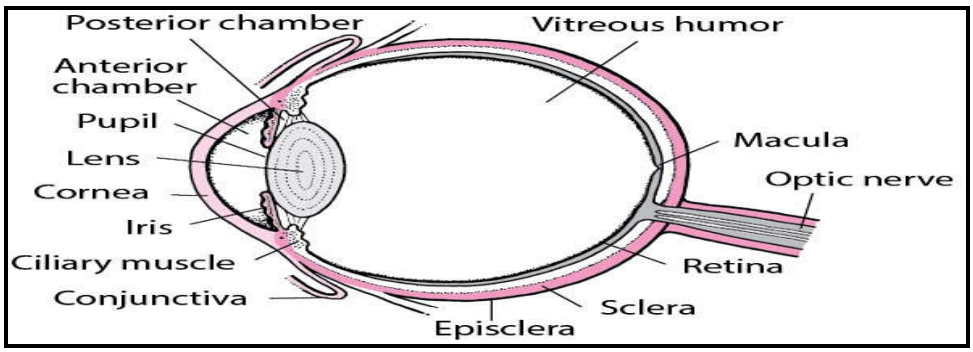
Rather than curcumin solution, nanogel loaded with curcumin shows AUC greater and improved BA and also enhances ocular permeation capacity. Dorzolamide formulated as nanocarrier in-situ gel with poloxamer 407 polymer as thermosensitive nano emulsion provides non-irritant and increased therapeutic efficient[25].

DENDRIMERS

Dendrimers are three-dimensional tree-structured macromolecules with nanoscalesize. The surface of dendritic molecules is easily functionalized with desired properties. Dendrimers can encapsulate hydrophobic drug molecules with the help of internal empty cavities and open conformation. Poly (amidoamine) PAMAM was the most widely used for the study of dendrimers as an ocular drug delivery system. Studies of PAMAM with drugs like pilocarpine, pucarin, etc. Novel phosphorus-containing dendrimers containing quaternary ammonium salt as core and carboxylic acid as terminal groups are synthesized. The properties such as easy surface functionalization and the ability to reason that dendrimers can be used in ODDS> However in animal studies, a vision blurring effect on the ocular surface has been observed after the dendrimers administration. This action should be modified in further studies[26].

Drugs used in combined strategies[20,21]

S.No	Drug	Method	Result
1	Diclofenac	Micelles in gel	Sustained release, No irritation effects, Low cytotoxic effects
2	piroxicam	Nanoparticles in-situ forming gel	Entrapment efficiency
3	meloxicam	Nano aggregates in contact lens	No irritation effect reduced corneal penetration



These formulations mainly target the anterior segment of eye diseases

Devices

CONCLUSION

Treatment of ocular diseases in an efficient manner could be a major challenge for scientists operating within the field of ocular drug delivery due to the nature of the ocular diseases, the distinctive structure of the attention, and barriers gift within the system; notably, the posterior ocular segments build the system unapproachable. Several attempts are created to boost ocular bioavailability by manipulating product formulation factors, like the use of mucoadhesive polymers. These approaches are found to be capable of accelerating the membrane contact time and up ocular bioavailability additionally. Therefore, it can be over that trendy technology appears to be logically explored in numerous ways that over the standard approaches, samples of non-conventional approaches being the employment of technology, microspheres, liposomes, applicable prodrug in place forming gel and therapy as effective means that of ocular drug delivery enhancing ocular absorption facet in conjunction with beside at the side of together with a reduction in side effects.

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CONFLICT OF INTEREST

We declare that we have no conflict of Interest.

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