Original Article

Ocular Drug Delivery: An Overview

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Abstract

The eye is a well protected organ. It has been regarded as a challenging undertaking to develop an effective treatment for ocular illnesses, particularly those affecting the posterior segment. Scientists have been challenged to identify other modes of administration, such as periocular channels, due to the limitations of the usual route of administration. Due of its potential to get around several difficulties with existing therapy, targeted medication delivery has attracted a lot of attention in the field. The use of nanotechnology in the treatment of a variety of ailments has shown great promise. Several innovative ocular drug delivery technologies, including microemulsions, nanosuspensions, nanoparticles, liposomes, nano-some, dendrimers, implants, and hydrogels, have been briefly discussed in this review. There is potential in the innovative medicine delivery technologies that are currently gaining traction.

Key Words:- Nanotechnology, Targeted drug delivery, Enhanced Bioavailability.

INTRODUCTION:-

Reaching the necessary of one of the most difficult tasks for pharmaceutical scientists to date has as been the delivery of medications into the eyes. The eye's distinctive structure prevents medication molecules from action. Anterior and posterior segments can be used to broadly categorise drug Reaching the necessary region of One of the most difficult tasks for pharmaceutical scientists to date delivery to the eye. Traditional methods, such as eye drops, suspensions, and ointments, cannot be regarded as the best in the treatment of ocular disorders that could jeopardise eyesight[1]. In contrast, over than 90% of the marketed Eye drops are the most common form of ophthalmic medications. These formulas focus mostly on the ocular disorders of the anterior segment [2]. The majority of medications used topically are removed from the body by washing Low ocular hydration is caused by a variety of mechanisms (lacrimation, tear dilution, and tear turnover).Medication bioavailability. Additionally, the human cornea contains substantia propria and epithelium. Moreover, the endothelium prevents medication molecules from entering the eye.Because of these elements Less than 5% of a drug's dose gets into the eye. Alternative methods, such as including Increasing the viscosity of solutions and using permeation enhancers/cyclodextrins did not result in any substantial development Following their inhibition or evasion, a considerable improvement in ocular medication absorption was achieved. Recently, numerous drug efflux pumps have been found. However, extended usage of these inhibitors may have negative effects[3]. For the formulation scientists, treating disorders of the posterior segment still represents an impossible undertaking. Drugs injected systemically cannot cross the blood-retinal barrier (BRB) and enter the retina[4]. The treatment of posterior segment illnesses necessitates high vitreal medication concentrations, which can only be achieved through local administration (intravitreal injections/implants and periocular injections). In comparison to intravitreal injections, periocular injections are linked to a relatively high level of patient compliance. Over the past ten years, significant advancements in the field of ocular medication administration have been noted. Understanding the numerous membrane transporters/receptors found on the eye has opened up new doors for growth. Targeted drug delivery methods make it simple to distribute drugs, especially polar ones that don't pass through ocular barriers[5].

Overview on anatomy and diseases affecting eye

In general, we examine the eye's structure under the following two headings: (a) anterior section and (b)rear portion. The front third of the eye, known as the anterior segment, is made up primarily of the pupil, cornea, iris, ciliary body, aqueous humour, and lens. The back three quarters of the eye, known as the posterior segment, are made up of the vitreous fluid, retina, choroid, macula, and optic nerve (Fig. 1).

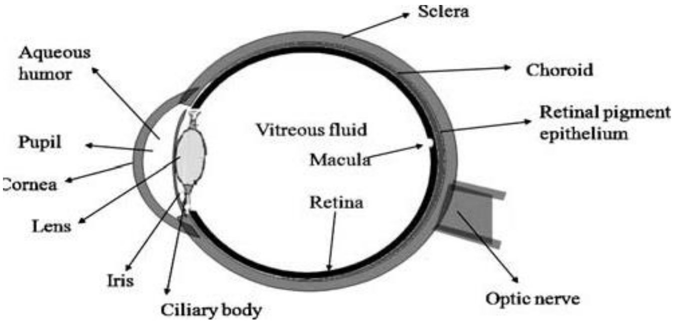


Figure I : Eye

NOVEL OCULAR DRUG DELIVERY SYSTEM

The science of medication delivery has made extensive use of colloidal carriers. Applications of nanotechnology in the treatment of a variety of disorders affecting the anterior as well as the posterior segment of the eye can be quite intriguing. It allows a more selective targeting coupled with continuous release of molecules at the targeted region. A perfect treatment would focus the active ingredient specifically at different conditions like CNV, diabetic retinopathy, and solid eye cancers. The retina lacks a lymphatic system, and the angiogenesis in this area of the eye resembles that of a solid tumour in terms of its effects on increased permeability and retention (EPR)[6].

The three major goals of medication delivery using nanotechnology-based products are as follows: (a) improve drug permeation (b) manage drug release (c) target drug[7].

ENHANCEMENT IN BIOAVAILABILITY:-

By increasing precorneal medication absorption and reducing precorneal drug loss, topical bioavailability can be made better.

Increasing viscosity:

Hydrophilic polymers like cellulose, polyalcohol, and polyacrylic acid are utilized as viscosity enhancers.One of the most significant mono adhesive muco-adhesion polymers is sodium carboxy methyl cellulose[8]. On the miotic response of pilocarpine, the effects of polyacrylic acid and polyacrylamide based hydrogels are examined. Hyaluronic acid offers a biocompatible and biodegradable matrix for fabrication of ocular sustained release dosage forms. Dosage forms based on the benzyl esters of hyaluronic acid were used for ophthalmic sustained release of methyl prednisolone. Carbomers were used as suspending or increasing viscosity agents in semisolid and liquid formulations. Hyaluronic acid was also used to prepare films and microspheres. It was discovered that polysaccharides like xanthan gum increased viscosity[9].Viscosity vehicles lengthen the contact period but have no discernible sustaining impact.

Penetration enhancers:

They work by altering the integrity of the corneal epithelium to increase corneal absorption. As potential penetration enhancers, chelating compounds, preservatives, surfactants, and bile salts were investigated[10].

Prodrugs:

Prodrugs alter the hydrophilic or hydrophobic properties of comeal drug transporters to increase drug's lipophilicity [11].The approach entails changing the molecular structure of the drug molecule, making it a safe method for delivering drugs to the eyes that is also selective and site-specific. Drugs such as epinephrine, phenylephrine, and others have improved penetration through prodrug formulations albuteroe, pilocarpine, and timolol[12].

Bio-adhesive polymers:

The residence duration of a medicine in the conjunctival sac is extended by these polymers because they stick to the mucin layer that covers the conjunctiva and corneal surfaces of the eye. These polymers may be natural, artificial, or semi-artificial. Commonly utilised synthetic polymers include polyacrylic acid, polycarbophil, and hyaluronic acid. A bio-adhesive vehicle appropriate for ophthalmic formulation is chitosan. Additionally referred to as bio-adhesive polysaccharides are xanthan and carrageenan[13].

ENHANCEMENT IN CONTROLLED DRUG DELIVERY:-

It is understood that the ideal method of ocular delivery would offer enhanced bioavailability, site-specific administration, and continuous drug release. Success has so been achieved in the following areas:

In situ forming gels:

Gel technology has advanced thanks to the creation of droppable gel. Upon instillation, they are liquid, and in the ocular cul-de-sac, they go through a phase transition to become viscoelastic gel, which gives a reaction to environmental changes[14]

Oil in water emulsions:

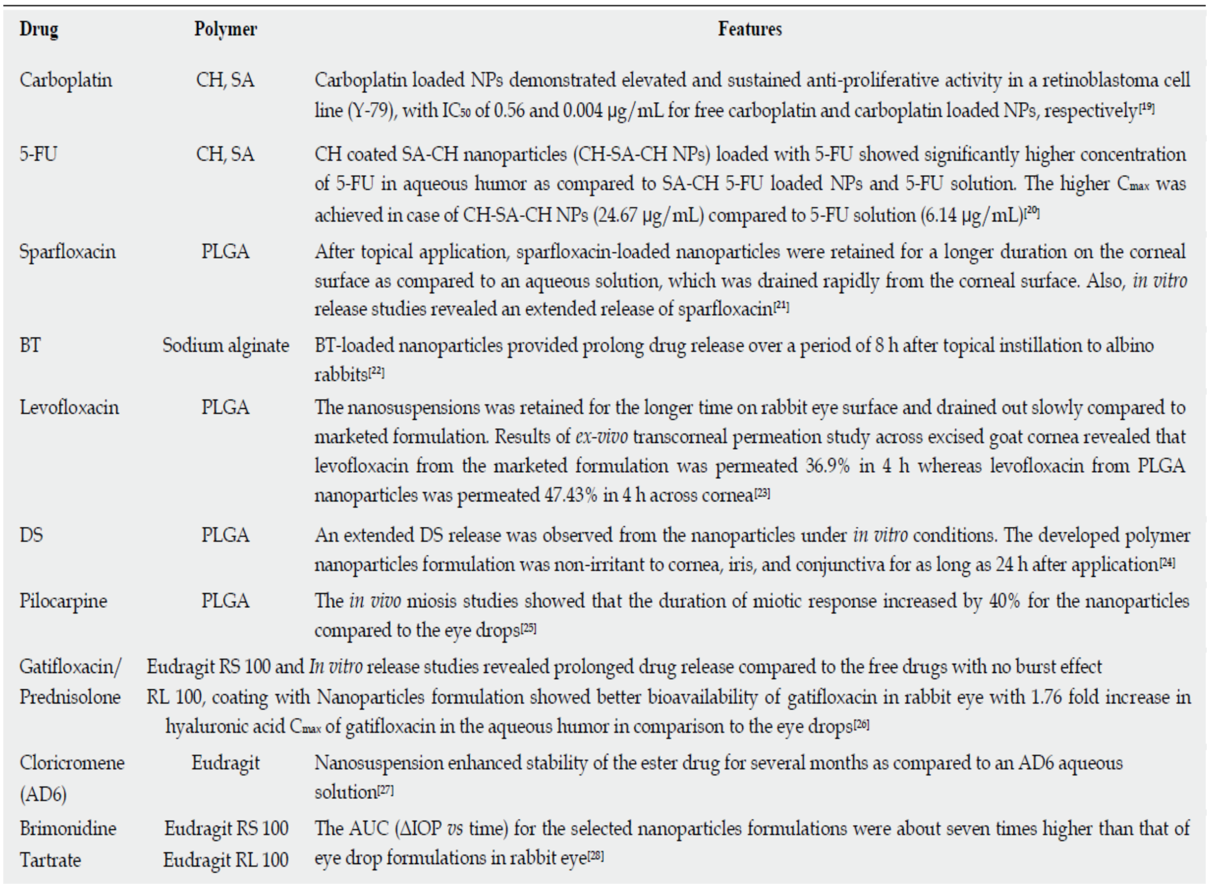
The emulsifiers were pluronics and phospholipids. The addition of antioxidants increased their shelf life. In contrast to a generic pilocarpine solution, which had a 5-hour half-life, a pilocarpine emulsion's 29-hour intra-ocular pressure-lowering impact was seen in rabbits [15]. Water-insoluble medicines that are solubilized in the internal oil phase can be delivered using oil in water emulsions.

COLLOIDAL CARRIERS:-

Nanoparticles:

Nanoparticles are described as particles having a diameter of less than 1 m and made up of different biodegradable or non-biodegradable polymers, lipids, phospholipids, or metals, according to Sahoo et al.[16] Depending on whether the medicine has been uniformly dispersed or coated within polymeric material, they can be categorised as nanospheres or nano-capsules. When kept in the cul-de-sac after topical administration, nanoparticles offer sustained release and prolonged therapeutic efficacy. The entrapped drug must be released from the particles at an adequate rate. Venous poly (alkyl cyanoacrylates), poly scapro-lactone, and poly (lactic-co-glycolic acid), which are hydrolyzed in tears, are the most often used polymers.[17] The ocular bioavailability of indomethacin was increased by a factor of two when it was coated with chitosan in poly (epsilon-caprolactone) nanoparticles. When poly (epsilon-caprolactone) nanoparticles were coated with polyethylene glycol, there was also increased permeability through the cornea[18]. For topical administration of gatifloxacin, mucoadhesive chitosan-sodium alginate nanoparticles were created and tested. With the help of this technology, there was a burst release within the first hour and a steady release for 24 hours. Because of the persistent activity seen after a single injection, this method aids in reducing the frequency of antibiotic dosing.

Table 1 Summary of recent developments with nanoparticles as ocular drug delivery vehicles



Drug	Polymer	Features
Carboplatin	CH, SA	Carboplatin loaded NPs demonstrated elevated and sustained anti-proliferative activity in a retinoblastoma cell line (Y-79), with IC_{50} of 0.56 and 0.004 µg/mL for free carboplatin and carboplatin loaded NPs, respectively[19]
5-FU	CH, SA	CH coated SA-CH nanoparticles (CH-SA-CH NPs) loaded with 5-FU showed significantly higher concentration of 5-FU in aqueous humor as compared to SA-CH 5-FU loaded NPs and 5-FU solution. The higher C_{max} was achieved in case of CH-SA-CH NPs (24.67 µg/mL) compared to 5-FU solution (6.14 µg/mL)[20]
Sparfloxacin	PLGA	After topical application, sparfloxacin-loaded nanoparticles were retained for a longer duration on the corneal surface as compared to an aqueous solution, which was drained rapidly from the corneal surface. Also, *in vitro* release studies revealed an extended release of sparfloxacin[21]
BT	Sodium alginate	BT-loaded nanoparticles provided prolong drug release over a period of 8 h after topical instillation to albino rabbits[22]
Levofloxacin	PLGA	The nanosuspensions was retained for the longer time on rabbit eye surface and drained out slowly compared to marketed formulation. Results of *ex-vivo* transcorneal permeation study across excised goat cornea revealed that levofloxacin from the marketed formulation was permeated 36.9% in 4 h whereas levofloxacin from PLGA nanoparticles was permeated 47.43% in 4 h across cornea[23]
DS	PLGA	An extended DS release was observed from the nanoparticles under *in vitro* conditions. The developed polymer nanoparticles formulation was non-irritant to cornea, iris, and conjunctiva for as long as 24 h after application[24]
Pilocarpine	PLGA	The *in vivo* miosis studies showed that the duration of miotic response increased by 40% for the nanoparticles compared to the eye drops[25]
Gatifloxacin/ Prednisolone	Eudragit RS 100 and RL 100, coating with hyaluronic acid	*In vitro* release studies revealed prolonged drug release compared to the free drugs with no burst effect Nanoparticles formulation showed better bioavailability of gatifloxacin in rabbit eye with 1.76 fold increase in C_{max} of gatifloxacin in the aqueous humor in comparison to the eye drops[26]
Cloricromene (AD6)	Eudragit	Nanosuspension enhanced stability of the ester drug for several months as compared to an AD6 aqueous solution[27]
Brimonidine Tartrate	Eudragit RS 100 Eudragit RL 100	The AUC (ΔIOP *vs* time) for the selected nanoparticles formulations were about seven times higher than that of eye drop formulations in rabbit eye[28]

CH:Chitosan; SA:saltalginate; 5-FU:5-Fluorouracil; PLGA:Lactide-co-glycolide polymer; IOP: Pressure within the eye; AUC: the area below the curve; BT: tartrate of brimonidine

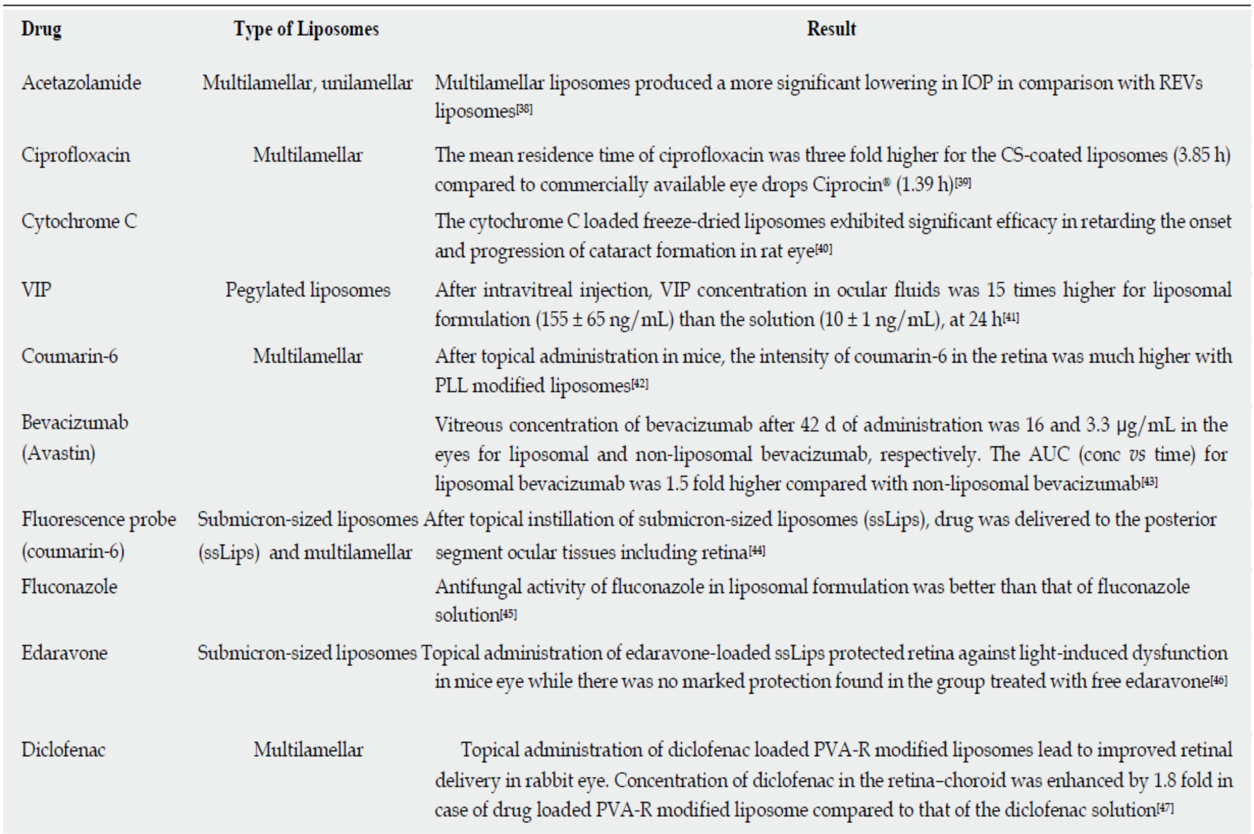
Niosomes:

Niosomes were first noted in the cosmetic industry in the 1970s by Vanlerberghe et al.,[29] Handjani-vila et al.,[30] and Van Abbe[31]. These researchers explained that non-ionic surfactants are preferred because their ability to irritate the skin decreases in the following order: cationic > anionic > ampholytic > non-ionic. Keller et al.[32], Green and Downs, According to Burstein[30], Kaur and Smitha[33], surfactants also serve as penetration enhancers by breaking functional complexes and removing the mucus layer, which may explain the improved ocular bioavailability of water-soluble substances trapped in niosomes. Niosomes are a viable drug delivery method for both hydrophilic and lipophilic medicines, according to Singh and Mezei. Timolol maleate, a water-soluble medication, was produced as both niosomes and discomes by Vyas et al.[34]. They discovered that discomes captured a higher amount of drug than niosomes (14% vs. 25%). Ghada abdelbary[35] and Nashwa el-gendy looked into the viability of using non-ionic surfactant vesicles as carriers for the ophthalmic controlled delivery of a water-soluble local anaesthetic. They found that the increase in ocular bioavailability was found to be approximately 3.07-fold compared to 2.48-fold in the case of niosomes for timolol maleate .Gentamicin sulphate, an antibiotic.

Liposomes:

Liposomes are lipid vesicles with an aqueous core that have been extensively used to transport various therapeutic molecules to the eye. Liposomes work best with lipophilic medicines and not hydrophilic ones. Ocular surfaces are a good fit for liposomes to adhere to and release their contents at the right times[36]. A higher affinity exists between positively charged liposomes to promote both Precorneal medication retention and bioavailability. Stearyl-amine was added to a liposomal formulation to improve dexamethyl valerate's corneal absorption. The negative surface charge of the mucin that covers the corneal epithelium may be more forcefully absorbed by the positive surface charge of the liposome. The precomea retention of liposomes is prolonged by coating them with bio-adhesive polymers. A longer duration of effect was demonstrated by pilocarpine-containing liposomes covered with carbopol 1342.Liposomes containing the antibiotic ciprofloxacin (CPFX) were created using multilamellar vesicles made from lecithin and alpha-L-dipalmithoyl-phosphatidylcholine to reduce tear-driven dilution in the conjunctival sac. Depending on the type of lipid composition chosen, this method achieved prolonged drug release[37].

Table 2 Recent advancements in liposomal ocular drug delivery



Drug	Type of Liposomes	Result
Acetazolamide	Multilamellar, unilamellar	Multilamellar liposomes produced a more significant lowering in IOP in comparison with REVs liposomes[38]
Ciprofloxacin	Multilamellar	The mean residence time of ciprofloxacin was three fold higher for the CS-coated liposomes (3.85 h) compared to commercially available eye drops Ciprocin® (1.39 h)[39]
Cytochrome C		The cytochrome C loaded freeze-dried liposomes exhibited significant efficacy in retarding the onset and progression of cataract formation in rat eye[40]
VIP	Pegylated liposomes	After intravitreal injection, VIP concentration in ocular fluids was 15 times higher for liposomal formulation (155 ± 65 ng/mL) than the solution (10 ± 1 ng/mL), at 24 h[41]
Coumarin-6	Multilamellar	After topical administration in mice, the intensity of coumarin-6 in the retina was much higher with PLL modified liposomes[42]
Bevacizumab (Avastin)		Vitreous concentration of bevacizumab after 42 d of administration was 16 and 3.3 μg/mL in the eyes for liposomal and non-liposomal bevacizumab, respectively. The AUC (conc *vs* time) for liposomal bevacizumab was 1.5 fold higher compared with non-liposomal bevacizumab[43]
Fluorescence probe (coumarin-6)	Submicron-sized liposomes (ssLips) and multilamellar	After topical instillation of submicron-sized liposomes (ssLips), drug was delivered to the posterior segment ocular tissues including retina[44]
Fluconazole		Antifungal activity of fluconazole in liposomal formulation was better than that of fluconazole solution[45]
Edaravone	Submicron-sized liposomes	Topical administration of edaravone-loaded ssLips protected retina against light-induced dysfunction in mice eye while there was no marked protection found in the group treated with free edaravone[46]
Diclofenac	Multilamellar	Topical administration of diclofenac loaded PVA-R modified liposomes lead to improved retinal delivery in rabbit eye. Concentration of diclofenac in the retina-choroid was enhanced by 1.8 fold in case of drug loaded PVA-R modified liposome compared to that of the diclofenac solution[47]

REVs: Reverse phase evaporation; PLL: Poly-L-lysine; VIP: Vasoactive intestinal peptide; PVA: Polyvinyl alcohol; IOP: Intraocular pressure; AUC: Area under the curve.

Micro-particulates:

They are micron-sized polymeric particles floating in a liquid media that carry drugs. The polymer backbone can physically spread drugs. Through diffusion, chemical reaction, and polymer degradation, the medication is released in the cul-de-sac; microparticles are larger than nanoparticles. There are chitosan microspheres loaded with acyclovir and pilocarpine-laden albumin or gelatin microspheres. Since microparticulate technology can be applied topically as an eye drop, patients are more likely to accept it[48].

Microemulsion:

In order to lower interfacial tension, surfactant and co-surfactant mixtures are used to promote the dispersion of water and oil into microemulsions. These solutions are frequently distinguished by greater thermodynamic stability, tiny droplet size (less than 100 nm), and clarity[49]. It has also been used to increase permeation over the cornea using microemulsion devices. Lecithin, propylene glycol, PEG 200, and isopropyl myristate have been used to create an oil-in-water solution that contains pilocarpine and is non-irritating to the rabbit animal model[50]. These formulations frequently offer continuous medication release, minimising the need for frequent dosing. In comparison to conventional eye drops, which must be administered four times per day, the microemulsion-based approach for pilocarpine reduces the frequency of administration to two times per day. This was caused by the surfactant-co-surfactant combination's augmentation of penetration.

Nanosuspensions:

Common colloidal carriers in nanosuspension products include inert polymeric resins. They aid in improving medication solubility and subsequently bioavailability. They are also well-liked since they are not irritants, unlike microemulsions. Flurbiprofen in the polymer resins eudragit RS 100® and RL 100® inhibits myosis, which could be brought on during extracapsular cataract surgery. Animal studies have shown that nanosuspensions have a stronger anti-inflammatory impact than micro-suspensions. Piroxicam in eudragit RS 100 was used in similar research. Significant anti-inflammatory benefits in comparison to micro-suspensions have been seen in in vivo investigations on rabbits[51].

Dendrimers:

Dendrimers are macromolecular substances with many branches circling a central core. They are a viable alternative vehicle for the administration of ocular drugs because of their nanosize, simplicity of synthesis, functionalization, and ability to connect numerous surface groups[52].

Iontophoresis:

Due to its non-invasive distribution method to both the anterior and posterior segment, ocular iontophoresis has recently attracted a lot of attention. To improve ionised medication penetration into tissue, a little electric current must be applied. The OcuPhorTM system has been built with an applicator, dispersive electrode, and a dose controller for transscleral iontophoresis (DDT), which can overcome the potential side effects related to intraocular injections and implants stated earlier[53].

Contact Lens:

The cornea is covered with contact lenses, which are thin, curved plastic disks[54]. Surface tension causes the contact lens to stick to the tear film covering the cornea after application. Drug-loaded contact lenses have been developed to deliver a variety of medications to the eye, including -blockers, antihistamines, and antimicrobials. It is hypothesised that the presence of the contact lens causes the drug molecules to spend more time in the post-lens tear film, increasing drug flux through the cornea while decreasing drug inflow into the nasolacrimal duct. Typically, contact lenses are soaked in medicinal solutions to load them with medication. These saturated contact lenses showed increased effectiveness in delivering medication as comparison to regular eye drops. Dexamethasone (DX) is bioavailable from poly (hydroxyethyl methacrylate) (PHEMA) contact lenses much more readily than it is from eye drops, according to Kim et al. Although these soaking contact lenses are more effective than topical drops, they have drawbacks related to insufficient drug loading and rapid drug release. Particle-filled contact lenses and molecularly imprinted contact lenses have been created to get around these problems. Gulsen et al. created particle-laden contact lenses for the ocular delivery of lidocaine. The medication is first entrapped in vesicles such as liposomes, nanoparticles, or microemulsion and then these vesicles are disseminated in the contact lens material. It has been proven that soft contact lenses made using the molecular imprinting technique have 1.6 times the capacity to load timolol than lenses made using a normal technique, and they also provide sustained timolol delivery[55]. In a different investigation, imprinted lenses with ketotifen fumarate showed better tear fluid bioavailability than drug-soaked lenses or eye drops with the drug. In comparison to non-imprinted lenses, the relative bioavailability of the imprinted lenses was three times higher. For imprinted lenses, non-imprinted lenses, and eye drops, the AUC values of ketotifen fumarate were 4365 1070 g/h per millilitre, 493 180 g/h per millilitre, and 46.6 24.5 g/h per millilitre, respectively[56]. The outcomes unequivocally show that imprinted lenses are more effective than non-imprinted lenses and eye drops.

CONCLUSION:-

These conditions and the presence of ocular barriers, particularly in the posterior ocular segments, treating ocular disorders effectively presents a daunting challenge to researchers in the field. The optimum course of treatment would keep the drug's efficacy for the following a single application, greater duration. Topical and intravitreal drug delivery cannot be regarded as secure, efficient, or patient-friendly. Many of these restrictions may be able to be overcome by periocular drug delivery, which can also offer sustained medication levels in ocular illnesses affecting both segments of the eye. For many pharmacological compounds, targeted distribution via the transporter can be an effective tactic. The current can be significantly enhanced using colloidal carriers. and may become an alternate therapy after being administered intraocularly.

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