OCULAR DRUG DELIVERY SYSTEM: CHALLENGES AND RECENT ADVANCEMENT

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ABSTRACT

The formulation for ocular drug delivery is always a challenging and tedious task for formulation scientist due to the presence of dynamic and static ocular barriers in the eye.Conventional ocular drug delivery includes topical eye drop which is one of the most suited and patient compliant prepared pharmaceutical products, intravitreal injection is another preferred route of administration. An ideal ophthalmic preparation must have good corneal penetration for maximum drug absorption to prolong contact time with ocular tissue and increase the bioavailability of the drug. Tear film along with cornea and conjunctiva and blood retinal barriers are major challenges discussed for anterior and posterior region. Novel approaches like nanoparticles, nano micelles, dendrimer, liposomes, and microneedle are studied for treatment of anterior and posterior disorders. *In situ* gels, iontophoresis, ocular implants, medicated contact lenses are pioneering inventions for sustained and controlled drug release along with their recent advancements and current innovations including use of microbots and 3D printing technology for treatment and diagnostic purposes are also discussed in this article. This review focuses on recent advancement of novel approaches and current innovation in ocular drug delivery technology.

keywords: Ocular drug delivery, Challenges in ocular drug delivery, Nanoparticles, Dendrimer, Liposomes, Microneedles, *in situ* gels, Iontophoresis, Microbots, 3D printing.

Introduction

Eye, a special organ with its own separate activities and complicated anatomical andphysiological structure. Its great variety of structures makes it difficult to create medicationdelivery devices for it. Eye drops used in the standard ocular medicine administration haveamajordrawbackin thatthey rapidly andcompletely clearedfrom theeye,which causesconsiderabledrugloss.[1][2].Onlylimitedamountofamedicine employed by

an eye drop reaches into the interior tissues of the eye from the corneallayer. [3][4]. The two types of ocular drug administration thatare focused on the anterior and posterior segments are derived from a broad taxonomy.Thetreatment of ocular diseases that have a serious impact on vision makes it undesirable to usetraditional pharmaceutical delivery techniques including eye drops, suspensions, and ointments.[5].

The main factors contributing to deteriorating vision in most developed countries areretinal illnesses including Diabetic retinopathy, the Age-Related Macular Degeneration (AMD),Retinalvasculardisorders[6].Therehavebeenseveralimprovementsin intraocular medicine delivery devices for eyes. Drawbacks of intra-vitreal injections have shown to minimize the socio-economic treatment load on the intra-ocular dose increaseinclinicaltrialsconductedforneovascularAMD[7][8].Recently,hydrogels, micro-needle,microbots and nanoparticles iontophoresis, dendrimer, In-situ gel, andpro drug approach have been researched with the use of tissue engineering. Because of thesustained drug release, elevated biocompatibility,and decline in biological drug degradation,thesesurfaceconjugate-modifieddrugdeliverymethodsincreasetheeffectivenessofdrugadministration and prolong intravitreal half-lives. [9][10]There have been studies into several periocular drug administration methods that are thoughttobe less enveloping than intra- vitreal injections. [11][12]

Ocular drug delivery barriers

Ocular surface drug loss: After administering the drug in its dosage form to the eye, lacrimalfluideliminatessomeofthesurfacedrugatamoderaterateof1l/min,whereasthemajoritydrugsare quicklyremovedthroughthenasolacrimalductwithin minutes.Drugeliminationcanalsocomefrom other routes, for instance absorption of drug in systemic circulation rather than ocularabsorption. Systemic absorption often occurs after the fluid has entered the nasal cavity and isdeliveredtothebloodcapillariesfrom theconjunctival sac.[13][14]

Lacrimalfluid-eyebarriersabsorption: Thecornealepitheliumfoundineyecanrestrictdrugabsorption present in lacrimal fluid. The penetration of the medication paracellularly is restrictedby tight junctions made of corneal epithelial cells. Drugs that are lipophilic have higher cornealpermeability thanthosethatarehydrophilic.Inotherwords,theconjunctivahasaleakierepithelium than the cornea and has rapid systemic absorption due to large surface area.[15]

Blood Ocular Barriers [BOB]: itshields the eye from foreign agents which exist in bloodstream.Blood-aqueous barriers and blood-retina barriers make up its two components. Uveal endothelialcells, or the layer of the eye between the iris, the sclera, the ciliary body, and the choroid, make upthe anterior blood-eye barrier. They inhibit admission of plasma albumin inside aqueous humour,inhibiting lipophilic drugs that

are present in plasma. The RPE and retinal capillaries that makeuptheposteriorbarrier,whichstandsin betweentheeyeandtheplasma,formatightwalljunction.Becausehighflowofblood&oozingchoroidalvasculatured rugsaresimplyaccessedoftheextra-vascular space of choroid, retinal endothelium & RPE hinder drug distribution in retina. [16][17]

Routes of ocular drug delivery

The common routes of ocular drug delivery are topical, intra-vitreal, intra-cameral,periocular,andsuprachoroidalandsubconjunctival.

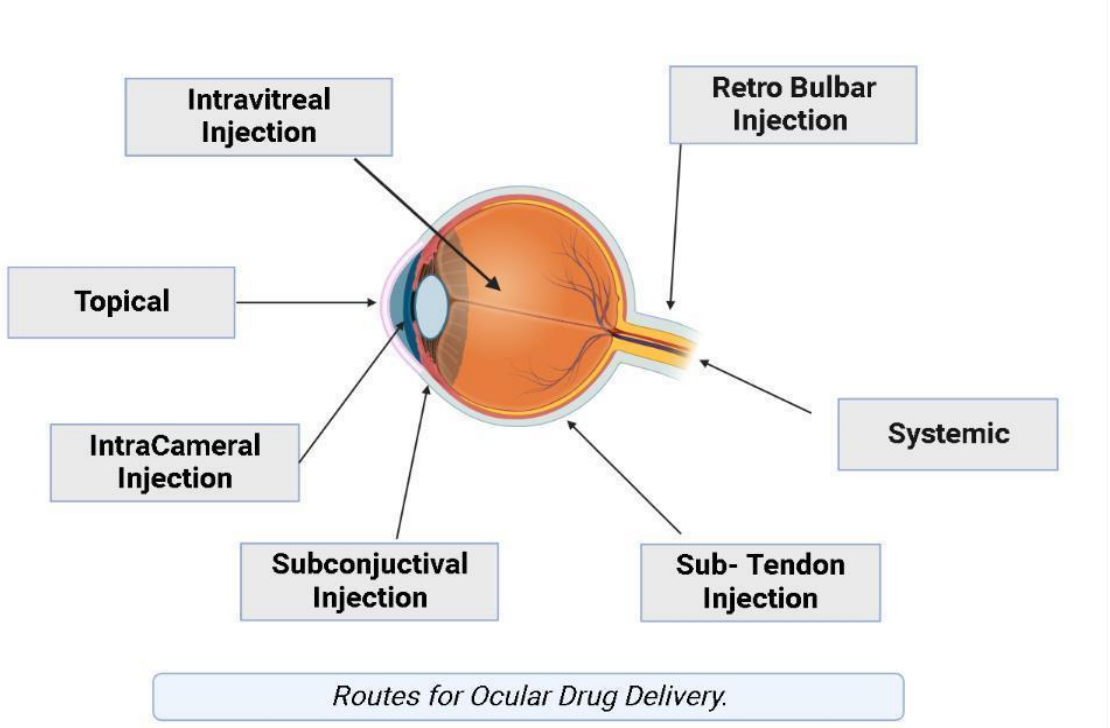

Fig. 1: Differentroutesforoculardrugdelivery.

[https://app.biorender.com/illustrations/637cdd953c871741df4a06e6]

Pros & cons of key routes of ocular drug delivery system

Route	Advantages	Disadvantages
Topical	• Noninvasive • Possibility of self-administration. • Patient compliance • It is feasible to deliver continuously for a day.	• Low bioavailability in the eye. • Nasolic Drainage • Epithelial protection • The posterior part is still not authorized or functional.
Systemic	• Noninvasive • Self-administration possible. • Patientconvenience.	• Low ocularbioavailability • Blood aqueousbarrier • Blood retinalbarrier • Systemic toxicity and side effects.
Periocular/ suprachoroidal	• Delivery possible forboth anterior and posterior segment • Possible depotsite	• Invasive • PatientInconvenience • Retinal pigmentepithelial (RPE) barrier for retinal delivery. • Potentialhemorrhage.
Intravitreal	• Effective retinaldelivery • Sustained delivery up to about 3years. • Bypass multiple ocular barriers.	• 100% vitrealbioavailability • Invasive • Patientinconvenience.

Table1: StatesaboutthePros &Consofdifferentoculardrugdeliverysystems[18]

Idealcharacteristicsofophthalmicdrugdeliverysystem[19]

- It shouldincrease the contact time with corneal tissue thus increasing ocular drugabsorption.
- Patient-friendlyeaseofadministration.
- Decreasedadministrationfrequency.
- Patientcompliancemustimprove.
- lessnegativesideeffectsandtoxicity.
- Minimizeprecornealdrugloss.
- Itshouldn'tirritatethepatient.
- Mustnotresultinblurredvision.
- Itmustbenon-greasyinnature.
- The proper concentrations and rheological properties of the viscous system.

Ocular diseases affecting anterior segment.

Table 2: Diseases affecting the anterior segment of eye.

Disease	**Caused by**	**Description**	**Treatment**	**References**
Dry eye	Imbalance b/w	The eyes are unable to generate high-quality tears to maintain	Cyclosporin Lubricating drops	[20][21]

	tear production absorption and drainage	thelubricationofeyesurface,aidintherecoveryofwounds,andguardagainsttheinfection.		
Blepharitis	Germs, skin sebum, and local allergic responses.	Blepharitistypicallyhastwotypes:ulcerativeandnonulcerative. A nonulcerative form associated with seborrhea of the face and scalp causes the ulcerative staphylococcal infection.	Bacitracin, erythromycin cream Oral antibiotics like macrolides	[22]
Conjunctivitis	infection caused by a bacterial or viral agent, such as the herpes simplex virus, pseudomonas aeruginosa, or staphylococcus	Thelossofcornealepithelium inadispersed,fine-punctatepatternisacommonindicator.Theusage of contact lenses, exposure to UV radiation, and adenovirus infection are the other riskfactorsforthis condition.	Azithromycin eye drops, gatifloxacin ophthalmic solution, gentamicin solution, Idoxuridine ophthalmic, ganciclovirophthalmic gel, Bepotastine besilate ocular solution	[23][24][25][26]

	aureus, respectively. Allergic responses			
Uveitis	Infection (TB), injury, autoimmune disease (AIDS)	Uveitis is an inflammation of the ciliary, choroid, and iris,	Corticosteroids, methotrexate,mycophenolate,azathioprine,andcyclosporine	[24]

Ocular diseases affecting posterior segment.

Table 3: Diseases affecting posterior segment of eye.

Disease	**Caused by**	**Description**	**Treatment**	**References**
Diabetic retinopathy	A significant, sight-threatening consequence of diabetes.	Tinybloodarteriesthroughoutthebodyareharmed bydiabetes,especiallythosein retina, blood and other substances leak from these tiny blood vessel causes diabeticretinopathy results in blurry or foggy eyes	Corticosteroids injections Laser surgery vitrectomy	[27]
Age-relatedMacularDegeneration(AMD)	Degeneration of the macular photoreceptor cell of the retina.	Two distinct kinds of AMD:non-neovascularAMD(dry)andneovascularAMD(wet).	Avastin (bevacizumab)and Lucentis (ranibizumab) - VEGF antibodies.	[28]

Challenges

A special issue developing a curative approach to establish a favourable concentration ofmedication at the primary location for right amount of time.The architecture, structure, and barrier function of the cornea must be considered to develop ocular delivery methods with high curative efficacy. To sustain a curative medication level in the tear film whileusingeyedrops, repeateddosageadministrationisnecessary.[29]

However, prolonged application of highly concentrated solutions causes adverse effects andcause damage at cellular level at eye's surface. The precorneal loss factors, such as solutiondrainage,lacrimation,teardynamics,teardilution,tearturnover,conjunctivalabsorption,non-productiveabsorption,lessretentiontimeinthecul-de-sac,andcornealepithelialmembrane imperviousness, are main barriers to anterior segment drug delivery after topicalapplication.

Due to these physical and physiological limitations, only one percent (1%) or less of the recommended dosage of the medication is absorbed by the eyes. Topicalformulations must balance lipophilicity and hydrophilicity with longer contact times tobeclinicallysuccessful.[30]

Challenges of anterior segment: topical treatment is often preferred over systemic therapy for eye disorders because any drugmolecule introduced via the ocular pathway must first clear precorneal barriers before reachinganatomical barrier of cornea. The tear film and conjunctiva are the first barriers that prevent anactivesubstancefromenteringtheeyequickly.[31]

Tear film:tear film is the main physiological barrier to medicines used topically. Theconjunctiva and cornea's first layer of defence is the tear film. It has the right balance ofnutrients,pH,andelectrolytesinadditiontomucin,proteins,andlipidsincombination.

The outermost lipid layer of tear film is 0.1 um thick and is produced by meibomian glands.The intermediate aqueous layer is 7–10 um thick, while the innermost mucous layer is 0.2-1.0um in thickness. Different eye glands as well as corneal epithelial cells release the materialthatmakesupthetearfilm.[32]

Conjunctiva:conjunctivaismostly preferredintraocularentrancepointfortopicallyadministered larger molecules & lipophobic compounds. However, rigid connections exist onthe apical side of the cells, conjunctiva which has a mucous membrane made of vascularizedepithelium thatis having thickness of 2–3 cell layers, gives a significantfunction as aprotective barrierontheocularsurface.[31]

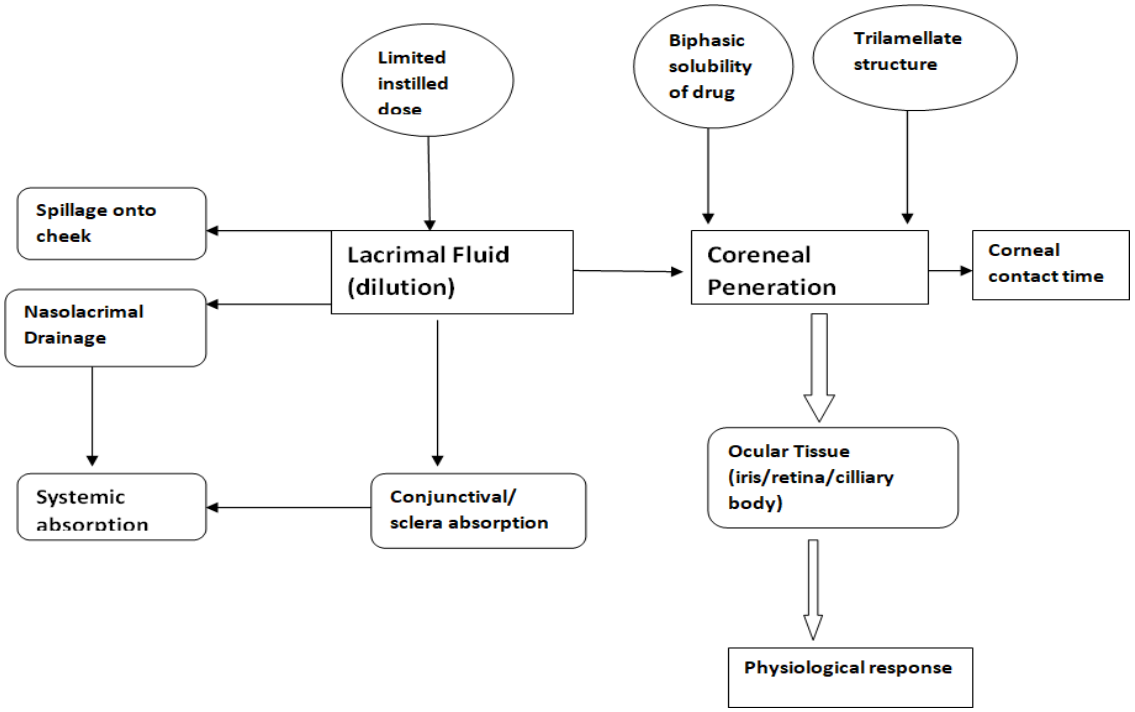

Fig. 2: DrugDistributioninocular tissues;the major reason why ocular dosage forms of drugs have a limited bioavailability is due toprecorneal loss causes. Additionally, to sustain therapeutic drug level inside tear film or at thesite ofaction,frequenteyedropadministration is need.[33]

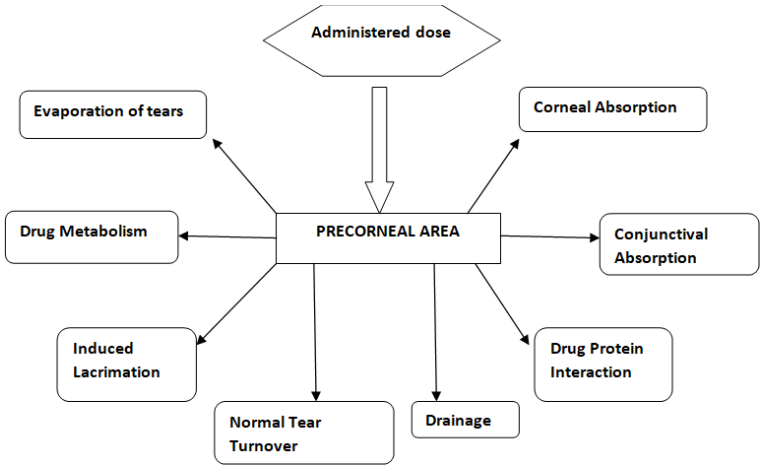

Fig. 3: Theprecornealcomponentsthataffecttheabsorption ofophthalmicmedications usedtopically.[29]

Challengesin PosteriorSegment

Blood-retinal barrier having high efficiency, topical ocular medicines cannot reach drug targetsin the posterior region (BRB). The same mechanisms that cause low ocular bioavailability alsoimpede medication delivery to the posterior region of ocular tissue. The BRB also reduces theefficiency of posterior medication administration via the intravenous method. [34] The BRB's tight connections prevent medicines given systemically from entering the retina.[35]High vitreal drug concentrations are required to properly treat diseases of the posterior segment. Drugadministrationintothelateralportionoftheeyeispredominantlycontrolled by BRB and lipophilic compounds are more permeable. As a result, large doses ofmedication are frequently administered, which can have adverse systemic effects. [36] Maintaining therapeutic medication concentration over extended times whilereducingthefrequencyofinjectionsisanotherissuefortheregion.

In Posterior route numerous drugs are eradicated at same time that they reach thesystemic circulationacross thebloodretinabarrier.

BloodRetinal Barrier (BRB): Hindrance established at the Retinal pigment epithelium cell surface is referred toas the outer BRB, and it controls some of the solute and nutrient flow from the choroid to thesub-retinal region. The inner BRB, like the BBB and is made up of microvascularendothelium that lines these arteries. Tight junctions, which connect these cells, allow for theincredibly selective passage of chemicals from blood to retina. This hindrance is needed forsustainingtheretina'sequilibrium.[37]

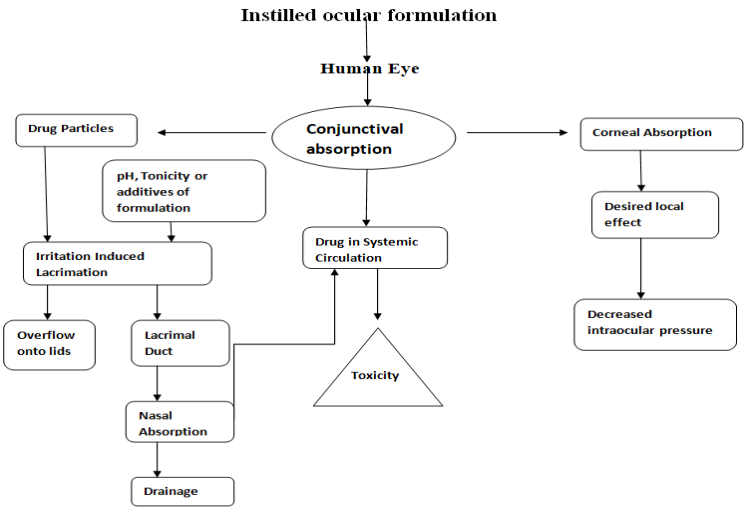

Fig. 4: Fateofophthalmicdrugdeliverysystem.[33]

Recent advancement in ocular drug delivery system

Dendrimers: are symmetric structures comprised of repeating branching molecules around acentral core. Polypropylenimines (PPI), poly-(amidoamine) (PAMAM), and phosphorousdendrimers are often preferred dendrimer for ocular administration.Most of the time,these are employed in ocular delivery systems to distribute nucleic acid- based medications. Theyare also employed in administration of hydrophilic and lipophilic drugs with low molecularweight for example antibiotics and antiglaucoma drugs. [38] [39]

It has been discovered thataltering the surface of the carrier by techniques like PEG-ylation orby acetylation, which further aidin lowering their toxicity aspects, can boost the carrier'sperformance. Thus, corneal residence time increases, improves bioavailability, and Prolongedtherapeutic effect are advantages of using dendrimers for topical treatments [39][40].

Auniquemethodtocreatelong-lastingintracellulardeliverysystemstodecreaseneuroinflammationistousedendrimer-basedtailoredintravitrealtreatmentinretinaldegeneration.

The dendrimers i.e., FITC and Cy5.5 are localised in the outer retina of two rat models of retinaldegenerations shown that these dendrimers are present for 35 days in the targeted cells afteradministration.

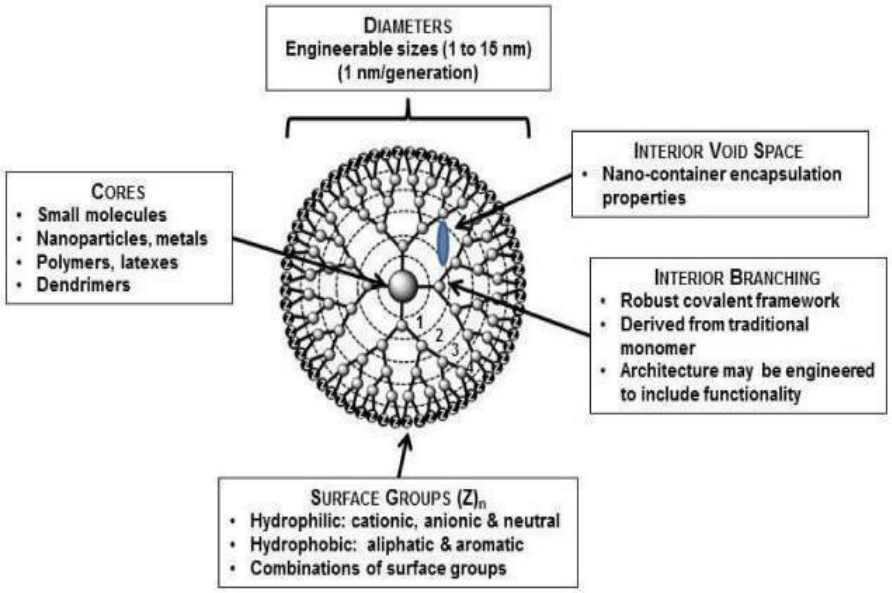

Fig.5: Dendrimersystemwiththespecificationsofdendrimerusedinoculardrugdelivery. [41]

Insitu*forminggel:Insitu*gelwasindeedanovelideadiscovered byresearchersintheearly1980s.*Insitu*geldrugadministrationto the ocular system is to enhance viscosity and reduce drug outflow from thecornea. When administered, the gel is liquid in nature, but as soon as it reaches the eye, itundergoesaphasetransitionandtransformsintoavisco-elasticgelthatreactstoenvironmentalchanges,instantlyincreasingthe drug'sbioavailability.

The main drawbacks of *in situ* gels are that they are sensitive to changes in temperature, pH,or ions. *In situ* gelling system instead of traditional eye drops gives a medicine a greater andlonger-lastingimpact.

In situ gels for ciprofloxacin were developed and tested by Eaga Chandra Mohan *et al.* [42], basedon concepts of ion activated system, thermally reversible gelation, and pH-triggered *in situ*gelation along with poly acrylic acid (Carbopol 940), which was used as the gelling agent. HPMC (1.5%) and Pluronic F127 (14%) were combined as the thermally reversible gelation. In order to produce excellent gels with HPMC integration, the amount of pluronic for *in situ* gelling property was decreased to 25% w/w. An anionic exocellular polymer produced by thebacteria Pseudomonas elodea, gellan gum (Gelrite) which induce gelation by cation activityandmakestheformulationstable,non-irritating,andtherapeuticallyeffective.Theheat-sensitivein-situgel-formingabilitiesofthenewcopolymerpoly(N-isopropylacrylamide)-chitosan(PNIPAAm-CS)anditsprospectiveuseforoculardrugadministrationwereexploredbyCao,Y.,*etal.* [42],in2007. Byusingthecloudpointapproach,thethermal sensitivity and LCST were calculated. The LCST of PNIPAAm-CS was 32°C, whichisequivalenttemperatureoneyesurface.

The finding pointed out, PNIPAAm-CS as a promising material for forming *in situ* gel & is heatsensitive as they also suggest that itmay enhance the bioavailability, effectiveness,andcompliance ofseveraleyemedications.

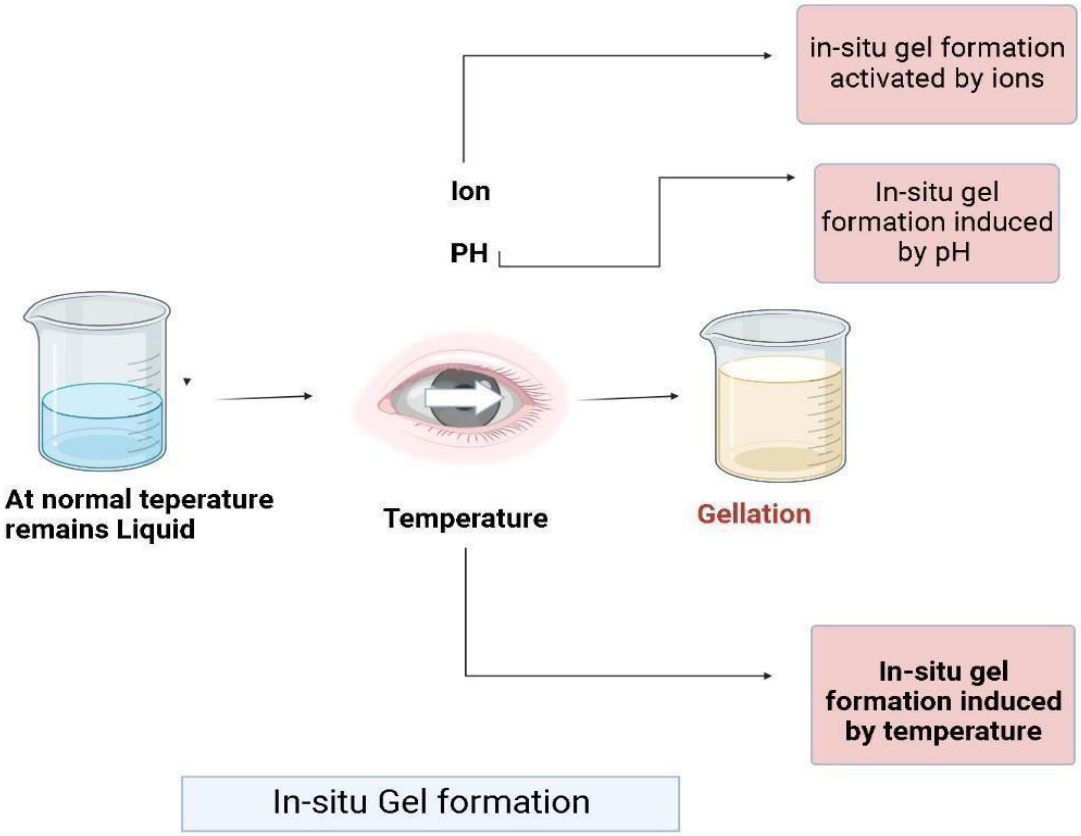

Fig. 6: *InSitu*Gelformation:differentfactorsinvolvedinconversionfromsoltogelformafter administrationofdosageform.

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Iontophoresis: this is a less painful method of administering medication to both the frontand posterior parts of the eye, ocular iontophoresis is one of the study areas that is expanding.Ionized medication delivery across membranes using a low electrical current is known asiontophoresis [43][44]. Drugs can pass membranes intwo different ways: via relocate and by electroosmosis. Iontophoresis can be categorised intotrans corneal,corneoscleral,ortransscleral.

The OcuPhor^{TM} system was developed which has an applicator, dispersive electrode, anddosage controller. Since the gadget distributes the active medication componentinto theretinochoroid region,asaresultitismoreeffective.Itcomesintransscleraliontophoresis.

Visulex^{TM}, enables targeted transport of ionised molecules through the sclera. Gentamycin,tobramycin, and ciprofloxacin are antibiotics that are successfully used; however, vancomycinis not due to its large molecular weight [45]. Drugs like dexamethasoneandantisenseODNshavebeenshowntohavefruitfuldeliveryresults

advantages:[46][47]

- It can mitigate the negative effects of intraocular implants and injections.
- It should be handledin a way thatmedicine is delivered quickly since there is a threatofburnsandachesduetohighcurrentdensity.
- Thelargemolecularweightdrugsof8000–12000.
- Ionicformispreferredwithasuitableconcentration.

Ocular inserts: Ophthalmic inserts are solid patches that, when inserted into the conjunctival sac of the eye, prevent the release of medications. Ocular inserts assist in resolving the problem of frequent dosing by efficiently maintaining drug concentration and providing controlled, sustained, and continuous drug administration.

The usage of ocular inserts has additional advantages, such as better medication absorption due to prolonged contact time, decreased dosage, and less frequent delivery. These systems' biggest drawbacks are patient disobedience, self-insertion challenges, and worry about inserts accidentally dropping into the eye. Ocular inserts can be hydrogel-like, soluble, and erodible thanks to a variety of production processes.[table 2] [48][49].

The delivery rate of the implant can be modulated by changing the polymer composition.J.Bourges*etal*. [50], implantscanbedeliveredemployingsolid,semi-solid,orparticulate-baseddeliverymethods.

Three phases of release of drug include preliminary burst, a medium diffusive phase, and aterminating burst of the drug. Polylactic acid (PLA), poly glycolic acid (PGA), and poly lactic-co- glycolic acid (PLGA) are examples of polymer which usually follows these stages duringdrugrelease.Theprolongedreleaseviaimplantsgainedenoughawarenessbymodificationsinrelease entities.[51]

Retisert: A non-biodegradable silicone laminated PVA implant is preferred for the treatmentof chronic uveitis. Although it significantly minimises uveitis recurrences and improves visionbutmaycausecataractformationandhighIOPhavelimiteditsusage.Itoffersasteady releaseoffluocinoloneacetonideforuptothree years.

Ozurdex:is animplantwith biodegradablenaturehaving FDA approval thatdistributesdexamethasoneforuptosixmonthsandisconstructedofaPLGApolymermatrix.

It helps in improving visual acuity in macular oedema, diabetic retinopathy, and Irvine gasssyndrome

S.NO.	**Type of Insert**	**Fabrication Polymer**	**Drug Release Mechanism**
1.	Erodible	Hydrophobic, Biodegradable	Erosion of surface
2.	Soluble	Hydrophilic, water soluble	Diffusion control or diffusion control based on solubility of drug.
3.	Osmotically driven	Hydrophilic and hydrophobic polymer mixture.	Due to change in osmotic gradient developed by drugs present in matrix system, tears flow in and drug is dispersed out through tears.
4.	Membrane controlled	Hydrophobic	The release is controlled by diffusion of drugs from core through hydrophobic membrane.

andposteriornon-infectious uveitis.

Table4: Differenttypesofocularinserts and drug release pattern [48]

Microneedles: the field of medicine has seen a rapid development of microneedles (MNs).With minimal damage, MN insertion into target tissuesestablishes temporarymicro pathwaysinbiologicaltissues.Themicropathwaysincreasedrugtransport,whichincreaseseffectiveness[52]

MNpatchesareofdifferentvarietieslikesomeofthemaremadeofelasticandwornasabandon the arms, others are flexible sheet types or pen shaped hollow MNs, impact springs like andinsertion of MN patches allocated with penetrating environments have all been developed toenhance manual application [53]. MNs are manually attached with thebacking thatassiststhedorsalskinbytheirstrengtheningandmakesiteasierforMN insertion.

MN treatment become unsuccessful when target inherent elasticity and irregular surfacespresentintargettissues.

MNs need to be subjected to a uniform and constant external force to enhance theirconsistent penetration into the appropriate depth. Manual MN insertion makes it challengingtoapplyconsistentandrepeatablestressestothetargettissues.ItbecameverydifficulttoapplyMNs in absence of the sufficientpressure and spherical shape and may also hinder theeffectivenessofdrugdelivery.

The tiny, delicate tissue taken from mouse cornea with a thickness varying from 68 to 137 μand a diameter of 2.6 mm. Models of suture-induced ocular angiogenesis have been used toevaluate the effectiveness of MNP therapy.the model drug rhodamine B dye (RB), was usedto evaluate medicine distribution after the MNP administration, and the lingering oedematousmodification was also recorded the next day. The development of Sunitinib Malate (SM)-loaded MNP systems followed an in vitro study that revealed SM's ability to reduce VEGF-induced angiogenesis. The reduction of corneal neovascularization was confirmed after theSM-MNP was applied to the suture-induced corneal angiogenesis paradigm.[54].

Another development in the administration of ocular drugs is the use of a rapidly detachablemicroneedlewithaporouswater-solublecoating.Highdemandexistsfordetachablemicroneedlesforthetreatmentofconditionsincludingkeratitisandglaucoma.Itoffersseveralbenefitsincludingminimuminvasionandconsistentmedicationadministration.[55].

Micro robotics:theeyeisthemostfascinatingorganwithinocularsystembecauseofhowdrugs are disposedofinit.Due toitseaseandsafety forocular chemotherapy, themostpreferredtechniqueistoadministerthedrugtopically..[56]

Amedicinal agent's oculardisposition andremoval dependon bothits physicochemicalcharacteristics and the pertinent physiology and anatomy of the ocular region. Therefore, acompleteunderstandingofthedrugandthelimitationsprovidedviatheadministrationroute(i.e.,ocular)necessaryforasuccessfuldrugdeliverysystem.[57]

In the past ten years,less painful treatment and diagnosis have become more and morecommon. The creation of innovative diagnostic and therapeutic systems with considerablebenefits over present approaches will be made possible by improvements in biomicrorobotics.Its potential to traverse physiological systems that would permit regional medicine distributionand sensing in areas of the body that are currently inaccessible or would need excessiveinvasivenesstoaccess.[58]

Microrobots provide a novel strategy for precise medicine delivery. They can deliver avarietyofloadsinapreciseandfastmannerduetotheircontrollabilityandpotentialforactivemovement in a liquid environment. In 2015, ETH Zurich researchers became the first to cureeyes with microbot technology which was further tested in anaesthetised rabbit eye. They madetubular microrobot with a sharp end which was propelled by magnetic field. Medicine is filledin the tubular body and its pointed end helped in propulsion due to the minimum friction in thefluidmedium.

EVA, silicon and PVA were used to make these devices the first two of which were perviousand reaching to a range of hydrophobic medications and latter of which was used to limit drugdiffusionthroughtheimplant.[59]

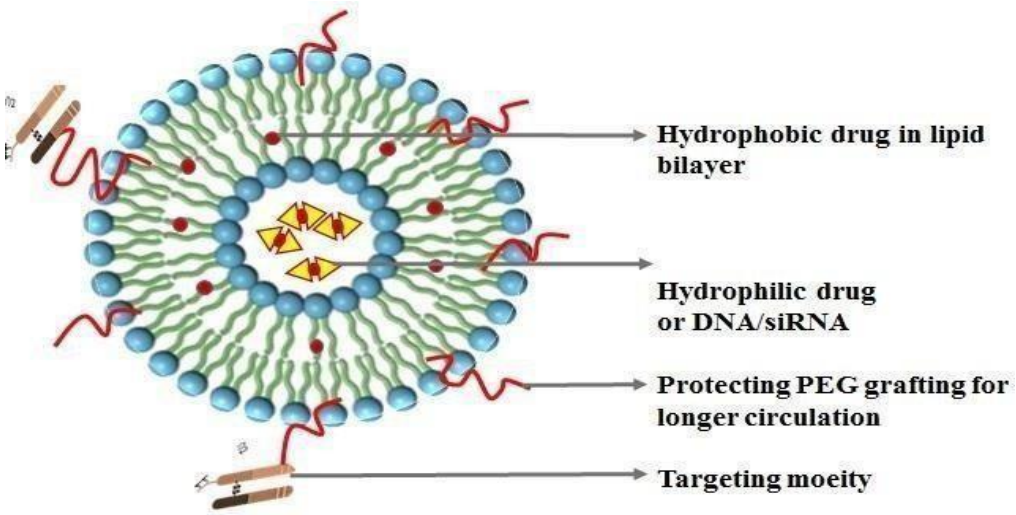
Biomicrorobotics,alsoknownasmicro roboticsforbiomedicalapplications,hasgainedattention as a potential remedy to some of the drawbacks of existing therapies. E.g., Lucentis(FDAapprovalin2012).[60]

S. No.	**Types of propulsion**	**Induced by**	**Mechanism of propulsion**	**References**
1.	Magnetic propulsion	Ferromagnetism and Para magnetism	Alteringthecurrentsflowingthroughtheelectromagneticcoils,themagneticfluxmaybechanged.	[61]
2.	Light propulsion	Laser light source	A laser wasusedtocontrolthefunctionallygradedarmsofamicrorobotbycausingthermalexpansion.The light intensity was changed to alter the step size.	[60]
3.	Chemical propulsion	Chemical reactions	A micron jet thatexploits bubbles of oxygen produced due to certainreactions inner part of jet tube along liquid media propels the component.	[60][62]
4.	Electric propulsion	Magnetic field manipulation	The micro-bot is provided with both attractive and repulsiveforces which eventually activate it and propulsion occur. The capacitive connections aids in driving microbots via electrodes present in the system.	[62]

Table 5: Types of propulsion system in microbots.

Liposomes: liposomes are synthetic vesicles with an aqueous core, one or more lipidbilayers, and are hence amphiphilic. Liposomes encapsulate drug molecule, and it does notdepend on physiochemical characteristic of the drug. Topical treatments with improvedcornealandconjunctivalpermeability,includingciprofloxacin,fluoroquinolone,andfluconazole,have beendevelopedusingliposomes.Inthepast,liposomeinjectionsare administered intravitreallyforretinaldisorders.[63]

Bevacizumab encapsulated in nanoliposomes was created and tested by Abrishami *etal.*[64],Accordingtotheirresearch,theintraocularspaceretainedanti-VEGFmedicationconcentration significantlygreaterthantheamountoffreebevacizumab.Alongwiththerapeutic compounds, siRNA encapsulated in liposomes demonstrated better**Fig. 7:** BasicStructureofliposomesusedinoculardrugdelivery.



[65]

Fig:7: intracellulardeliveryintheCNVmodel comparedtonakedsiRNA.[64]

3d printed punctal plugs in ocular drug delivery system.

Different approaches werediscussed above sections of this review like liposomes, nanoparticles, penetration enhancers,which extend the drug residence time or focus on promoting corneal penetration. Thus improvetheocularbioavailability,butmaintainingstabilityisachallenge.Iontophoresisandsonophoresisaretwophysicalforce-basedtechniquesthatprovidepotentialwaystotemporarily disrupt the barrier structures and improve penetration efficiency. Advanced drug-eluting devices, such as microneedles, drug-eluting contact lenses, and nano wafers, have beencreatedfortheefficientandprolongedreleaseofocularmedicines.[66]

Punctalplugsareatypical,non-invasivemethodoftreatingdryeyedisorders.Theyfunctionbyobstructingthecanaliculi,whichlinktheeyesandnoseandstoptearsfromdraining. [67][68]

Punctualplugsareusedintreatmentofpatientswithdryeyes,andthesearefoundtobemore efficientin terms of functional vision, osmolarity of tear, and stability of tear film.[69]

Table 6: Different types of punctal plugs.

S.No.	**Types**	**PolymerUsed**	**ReleaseTime**	**References**
1.	Permanentpunctalplugs	Polydioxanone,Polycaprolactone (PCL)	Twotosixmonths	[69]
2.	TemporarypunctalPlugs	Collagen	14days	[69]

3dprinting: Three-dimensional(3D)printingisanadditional manufacturingtechnologywhichis flexible and very beneficial in prototype development using techniques like computer aideddesign(CAD)software.

3Dprintingisemergingtechniqueprimarilyincludedinaerospace, foodindustry, robotics,andbiomedicine.

A variety of techniques, including as stereolithography (SLA), continuous liquid interface production (CLIP), digital light processing (DLP), and vat polymerization-based 3D printing, can be used to create 3D objects.

In pharmaceutical industry, it has created a unique identity due to its ability to produce smallbatches of personalized medicine, help in development of unconventional dosage form withtailoredreleaseconditionscanbeeasilyformulated.[70]

Punctal plugs containing drug dexamethasone was made using DLP 3D printing techniqueandhydrogelsmadeofpolyethylene glycoldiacrylate (PEGDA)usedformakingtheseplugs. Invitroreleasewasobservedin vitroocularflowmodelsimulatingsubconjunctival area.

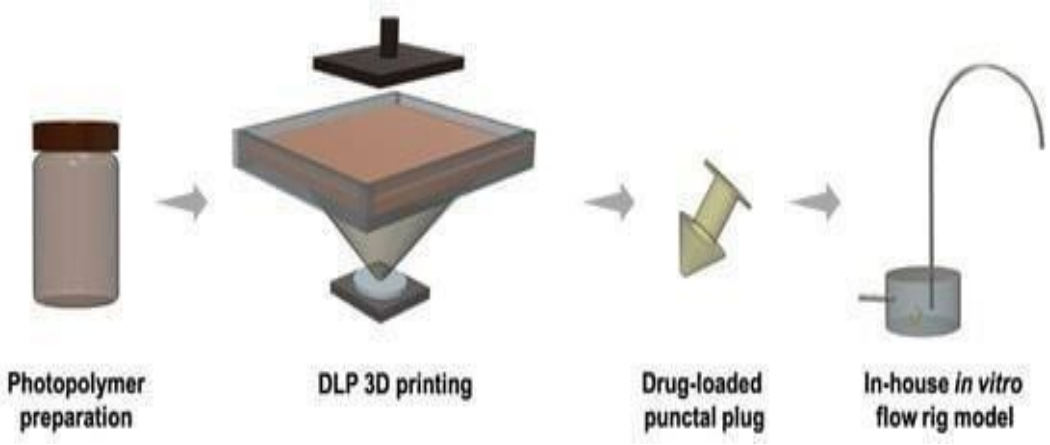


Fig. 8:DLP3Dprintingprocess [71]

Conclusion

This review discusses the challenges and obstacles in the paths of proposing a novelocular drug delivery targeting rug along with their possible remedies. Various ocular delivery barrierssuchasthe ocularsurfacebarrier,lacrimalfluideyebarrieralongwiththeblood-ocularbarrierhasbeendiscussed that needs to be overcome for designing new ocular drug delivery. The distributionissues to the anterior and posterior segments have been emphasized as a challenge in theocularmedicationsystemfordelivery.Therecentadvancementinthedendrimers, in-situ forming gel, iontophoresis, microneedles, micro robotics, microparticlesandnanoparticleswere discussed with their future potential and application to provide a better delivery system in ocular membranes. These innovative technologies and/or formulations also have a high precorneal residence period, no/minimal irritation, maintain drug release, and improve therapeutic drug bioavailability in the eye. A review of recent research developments in ocular drug delivery is necessary and beneficial for drug delivery experts to modify their thought processes and create innovative and secure drug delivery methods.

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