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Review Article

Nanotechnolgy a Novel Ocular Drug Delivery: A Review

Rainu Devi*, *Charanjeet Kaur, Vaishali Goel, Aman Kumar, Ujjwal Nautiyal*

Himachal Institute of Pharmacy, Paonta Sahib, Distt.Sirmour, HP, 173025

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ABSTRACT

Ocular drug delivery is one of the challenging tasks due to the unique structure of eye which restricts the entry of drug at the site of action. The protective mechanisms of the eye decrease the bioavailability of drug. Conventional ocular dosage form including eye drops are no longer sufficient to ocular diseases. There are most commonly available ophthalmic preparations such as drops and ointments when instilled into eye they are rapidly drained away from the ocular surface. So to overcome these problems newer pharmaceutical formulation such as nanoparticle, liposome, nanosuspension, microemulsion, iontophoresis have been developed to increase the bioavailability Utilization of nanotechnology presents new avenue of drug system development with potential to penetrate protective barriers and sustain ample tissue saturation. This review provides barriers of ocular drug delivery, summarizes recent findings and advantages of various nanocarriers systems like nanosuspensions, nanoparticles, nanocrystal in the field of ocular drug delivery and review also summarizes the various method of preparation for nanotechnology based ocular delivery.

1. Introduction

Ocular drug delivery has remained as one of the most challenging task for pharmaceutical scientists. The unique structure of the eye restricts the entry of drug molecules at the required site of action**[1]**. The ancient ophthalmic solutions, suspensions and ointment dosage forms are no longer satisfactory to give the therapeutic action as much as necessary to some current virulent diseases**[2]**.Topical application of drugs to the eye is the well established route of administration for the treatment of various eye diseases like dryness, conjunctiva, eye flu etc. The protective mechanisms of the eye such as Blinking, baseline and reflex lachrymation, and drainage decrease the bioavailability of drug and also help to remove rapidly foreign substances like the dust particles bacteria, including drugs, from the surface of the eye**[3]**.

There are many eye diseases which can be affected to the eye and also eye vision. Therefore marketed ophthalmic dosage formulations are classified as conventional and non-conventional (newer) drug delivery systems. There are most commonly available ophthalmic preparations such as drops and ointments about 70% of the eye dosage formulations in market. But these preparations when instilled into eye they are rapidly drained away from the ocular surface due to blinking tear flow and lacrimal nasal drainage of the eye. Only a small amount of drug is available for its therapeutic effect resulting in frequent dosing application to the eye. So overcome to these problems newer pharmaceutical ophthalmic formulation such as in-situ gel, nanoparticle, liposome, nanosuspension, microemulsion, iontophoresis and ocular inserts have been developed in last three decades increase the bioavailability of the drug as a sustained and controlled manner**[4]**.

The word Nanotechnology, arise from the Greek word nano meaning drawf, technology means application to the engineering, electronics, physical, material science, medical and manufacturing at a molecular and a submicron level. An early promoter of nanotechnology, Albert franks, defined it as that area of science and technology where dimensions and tolerance are in the range of 0.1-100nm**[5]**. Nanotechnology based ophthalmic formulations are one of the approaches which is currently being pursued for both anterior, as well as posterior segment drug delivery. Nanotechnology based systems with an appropriate particle size can be designed to ensure low irritation, adequate bioavailability, and ocular tissue compatibility. Several nanocarriers, such as nanoparticles, nanosuspensions, liposomes, nanomicelles and dendrimers have been developed for ocular drug delivery**[6]**.

1.2 Advantages of nanotechnology based ocular delivery

The various nanocarriers used for ocular drug delivery are Nanoparticles, Nanosuspensions, Microspheres, Micro-emulsion, liposome and dendimers. There are certain advantages of nanotechnology based drug delivery systems over other delivery systems especially in ocular drug delivery, using nanosuspension, nanoparticle it has a quicker onset of action, controls the rate of release, protect the drug against agents which cause degradation.

Corresponding Author: ***Rainu Devi****, Himachal Institute of Pharmacy, Paonta Sahib, Distt. Sirmour, HP, 173025; E-mail: renub4008@gmail.com

i. Nanocarriers such as nanoparticles have capacity to deliver ocular drugs to specific target sites. Different polymers are used in nanoparticle formulations**[7]**.
ii. The nanoparticulate nature of the drug shows sustained release effect by increasing its residence time in the cul-de-sac. The nanoparticles protect the drug against agents which cause degradation**[8]**.
iii. Nanosuspensions had a quicker onset of action and enhanced dose proportionality. Nanosuspensions also alter the pharmacokinetic parameters, improves the safety and efficacy of the drugs**[9]**.
iv. Nanotechnology can be used in drug delivery and gene therapy by applying novel self-assembled materials and devices of nanoscale size**[10]**.
v. Nanocarriers improve their interaction with the corneal and conjunctival epithelia and consequently their bioavailability**[11]**.
vi. Increase the residence time of the associated drugs onto the ocular surface and reduce the degradation of labile drug.
vii. Increased accurate dosing. To overcome the side effects of pulsed dosing produced by conventional system**[12,13].**

To improve the bioavailability, safety, and efficacy to reduce the side effect of the ocular delivery anatomy and extra ocular structure of eye is necessary.

2. Ocular structure

The eye is protected by several structures:

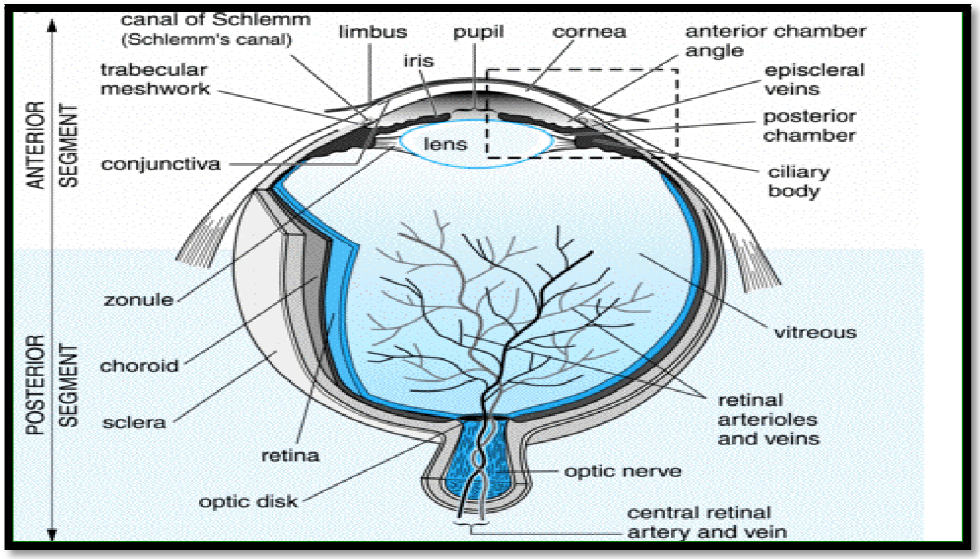

Figure No. 1: Anatomy of Eye**[15]**

1. Anterior Segment

1/3 portion of the eye occupied by the anterior segment while rest portion comes under posterior segment. Cornea, conjunctiva, iris, ciliary body and lens make the anterior portion of the eye.

2. Posterior Segment

Posterior segment of the eye include sclera, choroid, retinal pigment epithelium, neural retina, optic nerve and vitreous humor**[16,17].**

i. Eyebrows
ii. Eyelids and Eyelashes
iii. Lacrimal apparatus

Eyebrows protect the anterior aspect of eyeball from sweat, dust and foreign bodies. The eyelids have various layers of tissue including conjunctiva which protects the delicate cornea and front of the eye. When eye drops are administered, they are placed in lower conjunctival sac. The lacrimal glands secrete tears composed of water, mineral salts, antibodies and lysozyme a bacterial enzymes**[14]**.

2.1 Anatomy of eye

Eye is a spherical structure with a wall consists of three layers namely outer sclera, middle choroid layer and inner retina. Sclera is a tough fibrous coating that protects the inner layers. It is white except for the transparent area at the front, the cornea, which allows the light to enter the eye. The choroid layer, situated inside the sclera contains many blood vessels and is modified at the front of the eye as the pigmented iris. The biconvex lens is situated behind the pupil. The chamber behind the lens is filled with vitreous humor, a gelatinous substance occupying 80% of the eyeball at the back of the eye the light detecting retina. The human eyes are divided into anterior and posterior segment as shown in figure 1.

2.2 Routes of ocular drug delivery system

Absorption of drugs in the eye takes place either through corneal or non-corneal route. The selection of the route of administration depends primarily on the target tissue. There are three main routes commonly used for administration of drugs to the eye topical, intraocular and systemic. The topical route is the most common method to administer a medication to the eye. The intraocular route is more difficult to achieve practically. The advantages and disadvantage of different routes are shown in the table 1.

Table No. 1: Routes of ocular delivery with their advantages and disadvantages[18].

S.No	Routes	Advantages	Disadvantages
1.	Topical route	For eye drops	Poor patient compliance
2.	Sub conjuctivatl	Deliver drugs at the increased level to the uvea	Rapidly diluted, haemorrhage
3.	Intraviteral	Deliver the drug into the vitreous chamber	Positively charge restricted

2.3 Barriers of ocular drug delivery system

1. Drug Loss from the Ocular Surface

After the infusion of drug into the eye, the lacrimal fluid flow, remove the instilled or infused drug compound from the surface of eye. Even the lacrimal turnover rate is only about 1 micro litter per minute. Another method of non productive drug removal is its systemic absorption in the body instead of ocular absorption.

2. Lacrimal Fluid Eye Barrier

Corneal epithelium act as a barrier and limit the drug absorption from the lacrimal fluid into the eyes, there for, typically the lipophilic drugs have the higher permeability in the cornea as that of hydrophilic drugs. Generally the conjunctiva has the 20 times greater surface area then that of cornea.

3. Blood Ocular Barrier

Eye prevent from xenobiotics in the blood stream by blood ocular barriers. Mainly these barriers are divided into two parts:

Blood aqueous barrier – anterior blood eye barrier.
Blood retina barrier – posterior blood eye barrier**[19]**.

2.4 Classification of ocular drug delivery ststym

A multitude of ocular dosage forms are available for delivery of drugs to the eye. Liquids are the most popular and desirable state of dosage forms for the eye**[20]**. These can be classified on the basis of their physical forms as:

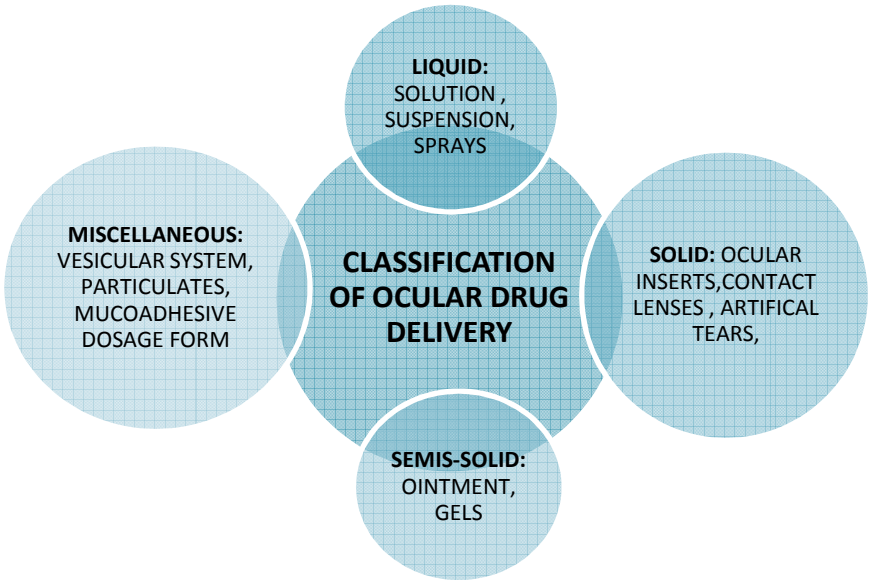

Figure No. 2: Classification of ocular drug delivery.

3. Nanotechnology in ocular drug delivery

The word Nanotechnology, arise from the Greek word nano meaning drawf, technology means application to the engineering, electronics, physical, material science medical and manufacturing at a molecular and a submicron level. Nanotechnology based ophthalmic formulations are one of the approaches which is currently being pursued for both anterior, as well as posterior segment drug delivery**[21]**. Nanotechnology based systems with an appropriate particle size can be designed to ensure low irritation, adequate bioavailability, and ocular tissue compatibility. Several nanocarriers, such as nanoparticles, nanosuspensions, liposomes, nanomicelles and dendrimers have been developed for ocular drug delivery. Some of them have shown promising results for improving ocular bioavailability**[22]**.

3.1 Different nanotechnolgy based ocular drug delivery

Nanoparticle

Nanoparticles are the particle with a diameter of less than 1µm, containing of various biodegradable materials, such as natural and synthetic polymer, liposomes, lipids, phospholipids and even inorganic material. Biodegradable nanoparticles of polymers like polylactides (PLAs), polycyanoacrylate, poly (d,l-lactides), natural polymers can be used effectively for efficient drug delivery to the effectively for efficient drug delivery to the ocular tissues**[23]**. Nanoparticles consisting of polymer matrices

were also proposed as promising systems for the topical administration of drugs onto the eye in the middle 80s. The first prototype of polymer nanoparticles used for this purpose was composed of poly-(alkyl cyanoacrylates) (PACA). Nanoparticles made of cationic and bioadhesive materials are probably those which have exhibited the greatest retention time at the ocular surface after instillation nanoparticles containing cyclosporine (CsA) using poly lactide co-glycolic acid (PLGA) and Eudragit RL-100 in combination or PLGA coated with carbopol for the treatment of severe dry eye syndrome. Nanoparticles of natural polymers which are made up of like sodium alginate, chitosan, are very effective in intraocular penetration for some specific drugs, because of contact time with corneal and conjunctival surfaces[24]. Nanoparticle suspensions, prepared from Eudragit RS 100 and RL 100 are reported to prevent myosis induced during extracapsular cataract surgery[25].

Nanosuspension

Nanosuspensions consist of pure, poorly water soluble drugs, suspended in an appropriate dispersion medium. Nanosuspension technology can be better utilized for drug compounds that form crystals with high energy content, which renders them insoluble in either organic (lipophilic) or hydrophilic media Polymeric nanoparticle suspensions, which are prepared from inert polymeric resins, can be utilized as important drug delivery vehicles, capable of prolonging drug release and enhancing bioavailability. Since these carriers do not irritate cornea, iris or conjunctiva, they act as an inert carrier for ophthalmic drugs[26]. Nanosuspensions can also used to achieve sustained release of the drug by incorporating or formulating with suitable hydrogel or mucoadhesive base or in ocular inserts. Flurbiprofen (FLU) loaded in polymeric nanoparticle suspensions, prepared from Eudragit RS 1001 and RL 1001 polymer resins are reported to prevent myosis induced during extra capsular cataract surgery. FLU is a non-steroidal anti-inflammatory drug (NSAID) that inhibits cyclo oxygenase and, thus, antagonizes papillary constriction during intraocular surgery[27].

Microemulsion

Microemulsion were first described Hoar and Schulman. Microemulsion is a dispersion of water and oil that formulated with surfactants and co-surfactants in order to stabilize the surface tension of emulsion. Microemulsion have a transparent appearance, with thermodynamic stability and a small droplet size in the dispersed phase (aqueous and nonaqueous phase) (<1.0μm). Microemulsions are an interesting alternative to ophthalmic formulation, due to their intrinsic properties and specific structure. They can be easily prepared through emulsification method, easily sterilized, and are more stable and have a high capacity for dissolving drugs. The ophthalmic o/w Microemulsion could be advantageous over other formulation, because the presence of surfactants and co-surfactants increase the dug molecules permeability, thereby increasing bioavailability of drugs. Due to, these systems act as penetration enhancers to facilitate corneal drug delivery. In 2002 the FDA approved the clinical use of an anionic emulsion containing cyclosporine A 0.05% for the treatment of chronic dry eye. non-medicated anionic emulsion for eye lubricating purposes, in patients suffering from moderate to severe dry eye syndrome (Refresh Dry Eye Therapy®, Allergen), and two lipidic emulsions, indicated for the restoration of the lipid layer of the lacrimal fluid (Lipimix™, Tubilux Pharma, and Soothe XP® Emollient Bausch and Lomb).The cationic nanoemulsions such as the product Cationorm® (Novagali Pharma, France) was launched in the European market for the treatment of dry eye symptoms[28].

Nano-crystals

Nano-crystals are nanoparticles, being composed of 100% drug without any matrix material, typically with a size range between 200 and 500 nm. Several methods are used to reduce the particle size of a drug—that is, bottom-up and top down technologies[29]. The striking advantage is that the drug nano-crystals can be applied by various administration routes, including ophthalmic administration, to create systems with prolonged retention times; moreover, they constitute a simple system—simple to produce and simple to use. Currently there are few studies investigating NSAIDs in the form of nano-crystals for ophthalmic application, because the major prerequisite for nanocrystal formulation is the hardness of the drug crystals. The striking advantage is that the drug nano-crystals can be applied by various administration routes, including ophthalmic administration, to create systems with prolonged retention times; moreover, they constitute a simple system—simple to produce and simple to use[30].

Dendrimers

Dendrimers are macromolecular compounds made up of a series of branches around an inner core. They are attractive systems for drug delivery because of their nanometres size range, ease of preparation and functionalization, and their ability to display multiple copies of surface groups for biological recognition processes. Because of these properties, they can be used as an effective vehicle for ophthalmic drug delivery[31]. The use of bioadhesive polymers, such as poly (acrylic) acids, to improve drug delivery and release by optimizing contact with the absorbing area in order to prolong residence time and decrease dosage frequency. These bioadhesive polymers, however, are associated with problems like blurred vision and formation of a veil in the corneal area, leading to loss of eyesight. To avoid these problems, dendrimers like poly (amidoamine) (PAMAM) are used[32].

4. Method of preparation

Nanocarriers such as nanoparticles, nanocrystal, and nanosuspension have applications in ophthalmology as they have capacity to deliver ocular drugs to specific target sites. Different polymers are used in nanoparticle formulations. Nanoparticles are prepared from different biodegradable polymers like poly(lactic acid),poly (alkyl cyanoacrylates) (PACA),poly(lactic-co-glycolic acid)(PLGA),poly(epsilon-caprolactone) (PCL),as well as different natural polymers like chitosan, gelatine, sodium alginate, and albumin can be used effectively for drug delivery to ocular tissues[33]. The different method used in preparation of nanocarriers for improvement of bioavailability as shown in figure:

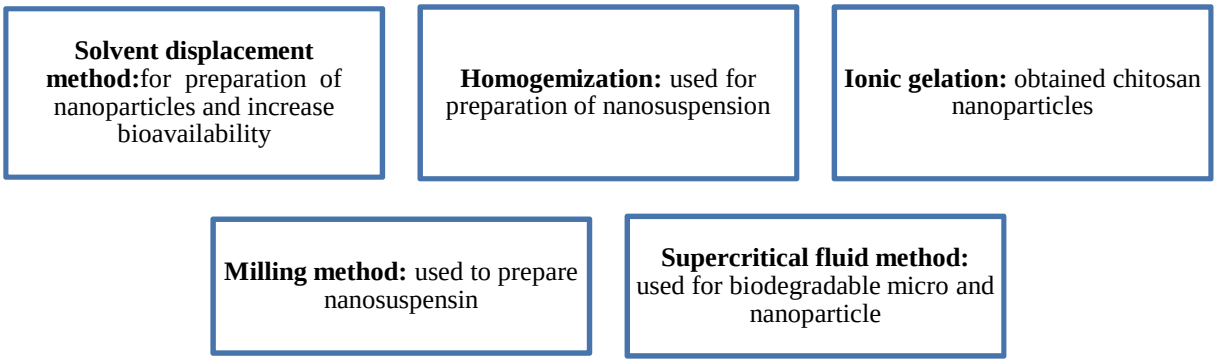

Figure No. 3: Method for preparation of nanotechnology based ocular drug delivery

Solvent displacement method called as nanoprecipitation method and has been widely used to prepare nanoparticles. Homogenisation is also used for preparation of nanosuspension. In milling method high-shear media mills or pearl mills are used to prepare nanosuspensions. Summary of methods used for preparation of polymeric nanoparticles for ocular delivery as listed in table:

Table No. 2: Method used for polymeric nanoparticle for ocular drug delivery.

Method	Drug	Category	Polymer	Stablizer	Referencers
Homogenisation	Prednisolone	Antiinflamatory	Hydroxy ethyl cellulose	Pluronic F68	**[34]**
Solvent displacement	Diclofenac	NSAID	Eudragit S100	Polaxamer 188nate	**[35]**
Ionic gelation	Mycophenolate mofetil	Immuno supperssant	Chitosan	Pluronic F68	**[36]**
Milling	Cyclosporine A	Immuno suppressant		Polyvinyl alcohol	**[37]**

5. Recent studies on nanotechnolgy based ocular drug delivery system

In a research Javadzadeh *et al.* formulated nanoparticles of naproxen with poly (lactic-co-glycolic acid) (PLGA) using single emulsion technique. Drug/polymer ratio, aqueous phase volume and speed of homogenization were considered as process parameters to achieve optimal preparation conditions. The study suggested the feasibility of formulating nanoparticles of PLGA with satisfactory physicochemical characteristics increases the anti-inflammatory effects of drug following its ocular or intra-joint administration**[38]**.

Hyaluronic acid (HA) or modified chitosan (CS) nanoparticles loaded with dorzolamide hydrochloride (DH) or timolol maleate (TM) for the treatment of glaucoma. The synergistic effect of Hyaluronic acid (HA) for mucoadhesion in association with chitosan provides sustained and local delivery of drugs to the ocular sites. It was revealed that CS-HA nanoparticles show higher reduction in intraocular pressure level as compared to drug solution. These results suggest that HA potentially enhance the mucoadhesiveness and efficiency of CS nanoparticles and may be promising carrier for ocular drug delivery**[39]**.

Yadav *et al.* reported the study of carvedilol loaded Eudragit E-100 nanoparticles by nanoprecipitation technique using poloxamer F- 407 as polymeric stabilizer and suggested the feasibility of formulated nanoparticles for treatment of hypertension. The prepared nanosuspension particle size ranged from 190nm-270nm. The nanoparticle size was found to be directly depended on Eudragit E-100 amount**[40]**.

In an investigation diclofenac loaded bio polymeric nanosuspension for ophthalmic delivery prepared by emulsion and solvent evaporation method using two different polymers poly[Lac(Glc-Leu)] (PLDA) and poly(lactide-co-glycoside) (PLGA). The study demonstrated the nanosuspensions enhanced corneal adhesion and stability during storage, especially at low temperature. The results indicated that nanosuspension could be utilised as potential delivery system for topical treatment of inflammatory conditions of eye**[41]**.

Pardeike *et al*. studied the newly secreted phospholipase A2 inhibitors PX-18 and PX-13 as drug nanosuspension prepared by high pressure homogenization. The formulated nanosuspension had been classified as safe for dermal and ocular application. It was observed that nanosuspensions with an active content of 5% (w/w) prepared by high pressure homogenisation technique produces particles in the nanometres size range. The results concluded that EPISKIN test and the HET-CAM test permits the classification of new secreted phospholipase A2 inhibitors that confirms PX-18 or PX-13 bulk material and their nanosuspensions were non irritant to the skin and eye**[42]**.

Ganciclovir (GCV) as antiviral drug loaded nanoformulations were prepared using reverse-phase evaporation technique for cytomegalovirus retinitis treatment. This study was done with to investigate the comparative potential of different

mucoadhesive nanoformulations for the topical ocular delivery of ganciclovir. Various nano-formulations which were prepared for the studies include GCV mucoadhesive nanoemulsions (GCV-NEs), chitosan nanoparticles (GCV-NPs) and GCV mucoadhesive niosomal dispersion (GCV-NDs). It was revealed from the results that the developed formulations were nonirritant and nontoxic in nature. It was further concluded that GCV nanoformulatios could be utilised as potential delivery system for treatment of ocular infections by topical instillation[43].

Econazole nitrate (ECO) loaded chitosan nanoparticles developed using sulfo butyl ether-β-cyclodextrin sodium as polyanionic cross-linker to achieve sustained therapeutic effect for ocular drug delivery systems. In vitro release of drug from nanoparticles was able to controlled 50% of the original amount released from nanoparticles upto 8 hrs. The in vivo studies suggest that, the chitosan loaded Econazole nitrate nanoparticles provide better antifungal activity as compared with Econazole nitrate solution. On the bases of results chitosan/sulfobutylether-β-CD nanoparticles were proved an effective candidate for ophthalmic delivery[44].

To improve the bioavailability and to prolong the residence time, Brimonidine tartrate (BT) loaded chitosan (CS) nanoparticles have been prepared by Singh et al. by ionic gelation technique. The formulated polymeric nanoparticles were evaluated by particle size, polydispersity index (PI), entrapment efficiency, DSC, SEM, TEM, which gave an insight of physicochemical interaction that influenced the CS nanoparticle formation. In vitro studies reveal the sustained release effect of BT nanoparticle over the period of 4 hrs in saline phosphate buffer pH 7.4. The structural interactions between BT, TPP and CS matrix were demonstrated by DSC. The results concluded that dosage frequency was reduced by sustained drug release from CS Nanoparticles in the treatment of glaucoma[45].

Adibkia *et al*. prepared Eudragit RS100 loaded piroxicam nanoparticles using similar method for control the inflammatory symptoms in rabbits with endotoxin-induced uveitis (EIU). The study suggested the non-invasive implementation of the piroxicam- Eudragit RS-100 nanosuspensions as a safer controlled ocular delivery of anti-inflammation agents for inhibition of the uveitis symptoms[46].

Chitosan loaded Cyclosporine A (CsA) nanoparticles were formulated by Campos *et al*. by ionic gelation method for improvement of delivery of drugs to ocular surface. The polydispersity index of CsA loaded chitosan nanoparticles was found to be 0.34. In vitro release studies revealed that during the first hour a fast release was observed followed by a more gradual drug release during a 24 hrs period when performed under sink conditions. In vivo experiments revealed that, it was possible to achieve therapeutic concentrations in cornea and conjunctiva during at least 48 hrs on topical instillation of nanoparticles to rabbits. The nanoparticles are proved to be an excellent vehicle in enhancing the therapeutic index of clinically challenging drugs with potential application at extra ocular level[47].

6. Application of nanotechnogy based ocular drug delivery

An exciting challenge for developing suitable drug delivery systems targeted for ocular diseases is one of the major focuses of pharmaceutical scientists. There are several nanocarriers' delivery systems under investigation such as: micro particles, nanoparticles, liposomes, and dendrimers. Polymeric nanoparticles are also able to target diseases in the posterior segment of the eye such as age-related macular degeneration, cytomegalovirus retinitis, diabetic retinopathy, posterior uveitis and retinitis pigmentosa. Nanosuspensions had a quicker onset of action and enhanced dose proportionality. The application of different nanocarriers as shown below:

Table No. 3: Typical nanotechnology-based strategies for ocular anterior diseases application.

S.No.	Formulation	Material type	Payload	Size(nm)	Function	References
1.	Nanoparticle	Chitosan	Gene	~200	Superior transfection efficiency	[48]
2.	Nanosuspension	Polymer	Diclofenac	105	Enhanced penetration	[49]
3.	Liposome	Polymer	Coenzyme Q110	100-120	Increase the activity of superoxide	[50]
4.	Dendimers	Polymer	Gene	~50	Effective gene transfection in RPE cells	[51]
5.	Nanoparticle	Polymer	Flurbiprofen	100	For anterior diseases segment	[52]
6.	Hydrogel	Polymer	Mitomycin C	80	Good compatibility	[53]

7. Conclusion

The novel advanced delivery systems offer more protective and effective means of the therapy for the nearly inaccessible diseases or syndromes of eyes. Drug delivery by topical and Intravitreal routes cannot be considered safe, effective In recent years, scientists have focused on designing a strategy with a multidisciplinary approach e.g. micro needle, microemulsion, nanosuspension, iontophoresis and MRI. This review focused on nanotechnology based ocular drug delivery such as nanoparticle, nanosuspension, nanocapsule, dendimers to increase the bioavailability and protect from eye barrier. The nanoparticulate nature of the drug shows sustained release effect by increasing its residence time in the cul-de-s. Nanosuspensions also alter the pharmacokinetic parameters, improves the safety and efficacy of the drug. Nanosuspensions can also used to achieve sustained release of the drug by incorporating or formulating with suitable hydrogel or mucoadhesive base or in ocular insert. Nanocarriers improve their interaction with the corneal and conjunctival epithelia and consequently their bioavailability

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