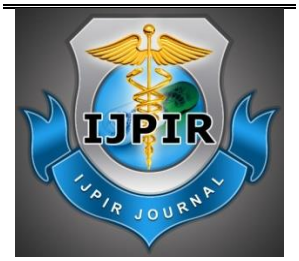
Research Article



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Nano sized ocular drug delivery system - an overview

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ABSTRACT

Drug delivery to the eye has remained as one of the most challenging research for formulation scientists as ocular drug delivery system requires a series of specified characteristics according to the physiological structure of the eye. Eye is a unique and challenging organ for therapeutic drug delivery on to the surface as well as in the interior part of the ocular structure.The drug may bind to tear proteins and conjunctival mucin to treat the local ophthalmic diseases, liquid eye drop is the most desirable dosage form when considering convenience of administration and clinical compliance of the patients. These conventional dosage forms account for nearly 90% of the currently available marketed formulations owing to their simplicity and good acceptance by patients. However, conventional eye drops, most of which are present in the solution form, usually have quite a limited therapeutic efficacy due to the low bioavailability The use of nano-approaches like nano-suspensions, nanoparticles, Nano emulsion, niosomes and liposomes has led to the solution of various solubility and permeability related problems of poorly soluble drugs like dexamethasone, cyclosporin, dorzolamide, gancyclovir and many more drugs. This review includes various nano sized formulations used to achieve prolonged contact time of drugs with the cornea and increase their bioavailability. Ophthalmic drug delivery is one of the most interesting and challenging endeavors facing the pharmaceutical scientist.

Keywords: Ocular drug delivery nano-suspensions, Nanoparticles, Nano emulsion, Niosomes and liposomes

INTRODUCTION

The development of drug delivery approach for the transportation of drug in a bio-available and safe manner to the target site is now becoming an exceedingly important area of bio-pharmaceutical researches. To be sure, a large number of novel drug delivery technologies surface every year and every segment of body part has been attempted as a potential target for the site of action. As a consequence, various smart drug delivery technologies with significant outcomes have been reported for BCS class-II and class-IV drugs,

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peptides, proteins, etc. Further, among novel drug delivery technologies, advancement of nanotechnology in formulation development for bio-degradable, non-biodegradable, nanoemulsions, nanoparticles, vesicular systems, implants, bioadhesive systems, etc are currently under intensive exploratory studies **[1]**.Typically, less than 5% of the drug applied penetrates the cornea/sclera and reaches the intraocular tissue, with the major fraction of the dose applied often absorbed systemically through the conjunctiva and nasolacrimal duct. On the other hand, corneal and conjunctival epithelia of human eye, along with the tear film, construct a compact barrier preventing the drug absorption into the intraocular area. This can result in low bioavailability and undesirable systemic side effects **[2].** In this review, we presented the application of various nano-approaches in the field of topical ophthalmic drug delivery attempted by numerous investigators over the last decade. Review also enlightens the amalgamation of mucoadhesive characteristics with nanotechnology for the enhancement of corneal residency and bioavailability. Furthermore, topical ocular delivery research is also summarized in the initial of the article.

CONVENTIONAL APPROACH

Conventional dosage forms such as solutions, suspensions and ointments account for almost 90% of the currently accessible ophthalmic formulations on the market **[2]**. They offer some advantages such as their ease of administration by the patient, ease of preparation and low production costs. However, there are also significant disadvantages, especially with the use of conventional solutions, including the very short contact time with the ocular surface and the fast nasolacrimal drainage, both leading to poor bioavailability of the drug. Nevertheless, conventional eye drops remain the most commonly used dosage forms in ocular delivery.

Solutions

The reasons for choosing solutions over other dosage forms include their favorable cost, simplicity of formulation development and production, and high acceptance by the patients **[3]**. However, they also exhibit major drawbacks, such as rapid and extensive pre-corneal loss, the high absorption via the conjunctiva and nasolacrimal duct leading to systemic side effects, as well as increased instillation frequency resulting in low patient compliance. Some of these problems have been reduced by the addition of viscosity-enhancing agents such as cellulose derivates, which are believed to increase the viscosity of the preparation and consequently reduce the drainage rate.

Suspensions

Suspensions of the micronized drug [<5µm] in a suitable aqueous vehicle are formulated, where the active compound is water insoluble. It is assumed that the drug particles remain in the conjunctival sac, thus promoting a sustained release effect **[4].** According to Davies topical ophthalmic suspensions have a number of limitations **[5]**. They need to be adequately shaken before use to ensure correct dosing, and the amount of drug required to achieve therapeutic benefit, only a moderate increase in bioavailability, rendering suspensions expensive in terms of their production costs **[6]**.

Ointments

Ointments generally consist of a dissolved or dispersed drug in an appropriate vehicle base. They are the most commonly used semisolid preparations as they are well tolerated, fairly safe and increase the ocular bioavailability of the drug. On application, ointment breaks up into small oily droplets that remain in the cul-de-sac as a drug depot. The drug eventually gets to the ointment-tear interface due to the shearing action of the eyelids **[7].**

Viscosity enhancing systems

In order to reduce the lachrymal clearance of ophthalmic solutions, various polymers have been added to increase the viscosity of the conventional eye drops. Among the range of hydrophilic polymers investigated in the area of ocular drug delivery are polyvinyl alcohol [PVA] and polyvinyl pyrrolidone [PVP], cellulose derivatives such as methylcellulose and polyacrylic acids [Carbopols®]. [**8]**

In situ gelling systems

In situ gelling systems are viscous polymer-based liquids that exhibit sol-to-gel phase transition

on the ocular surface due to change in a specific physico-chemical parameter [ionic strength, temperature or pH]. They are highly advantageous over preformed gels as they can be easily instilled in liquid form, but are capable of prolonging the residence time of the formulation on the surface of the eye due to gelling **[9]**.

NANOMEDICINE APPROACH

The use of nano-approaches like nano-suspensions, nanoparticles, nanoemulsion, niosomes and liposomes has led to the solution of various solubility and permeability related problems of poorly soluble drugs like dexamethasone, cyclosporin, dorzolamide, gancyclovir and many more **[10]**. Drugs can also be targeted to ocular tissue to allow region specific delivery and minimize side effects to other organs **[11]**. Besides this, depending on their particle charge, surface properties and relative hydrophobicity, nanoparticles can be designed for successfully overcoming corneal barriers. In addition to these points, encapsulation of drug in nanoparticles, nanospheres, liposomes etc, can also provide stability to the drug along with prolonged exposure of the drug by controlled release behaviour **[10]**.

The use of nano-approaches like nano-suspensions, nanoparticles, nanoemulsion, niosomes and liposomes has led to the solution of various solubility and permeability related problems of poorly soluble drugs like dexamethasone, cyclosporin, dorzolamide, gancyclovir and many more. **Table-1** summarises the recent works on nano-approaches for drug delivery used in ophthalmic research.

Nanoparticles [NPS]/ Nanospheres/ Nanocapsules

Nanoparticles are sub-microscopic, colloidal system consisting of macromolecular substances that vary in size from 10 nm to 1000 nm. The drug may be dissolved, entrapped, adsorbed, attached or encapsulated into the nanoparticle matrix. Depending on the method of preparation, nanoparticles, nanospheres or nanocapsules can be obtained with different properties and release profile for the encapsulated drugs **[10]**.

Chitosan Nanoparticles

Natural cationic polymer chitosan [CH] nanocarriers have attracted a great deal of attention because of its unique properties, such as acceptable biocompatibility and biodegradability.Chitosan [CH] is a cationic polysaccharide able to gel when it comes in contact with specific multivalent polyanions, such as sodium tripolyphosphate [TPP]. Nanoparticles are spontaneously formed upon mixing of CH and TPP solutions, through the formation of inter- and intramolecular linkages between the phosphate groups of TPP and the amino groups of CH **[12]**.

Albumin Nanoparticles

Ganciclovir [GCV] loaded albumin nanoparticles for the treatment of cytomegalovirus retinitis. Its in-vitro studies indicated a burst release of the drug in 1 h, which continued in a sustained manner for 5 days and continued for almost 30 days. The result demonstrated its controlled delivery for longer period [**13]**.

Gelatin Nanoparticles

Due to its biocompatible and biodegradable nature, its nanoparticles were studied as nano-sized ocular drug carrier. The developed formulations were studied for various characteristics like particle size, zeta potential, encapsulation efficiency, in vitro drug release. All particle sizes of pilocarpine HCl and hydrocortisone loaded gelatin nanoparticles were obtained in the range 300–500 nm and 110–220 nm, respectively. The average zeta potential value for particles prepared at pH 6 equals −6.95 mV, for spheres prepared at pH 4 it amounts to −6.10 mV. Consequently, there is no significant effect of the preparation pH on zeta potential value of the particles obtained. But in case of hydrocortisone, zeta potential was found to be between −4 to −12 mV that showed significant influence of gelatin on the zeta potential value **[14]**

Alginate Nanoparticles

The potential of sodium alginate nanoparticles has been explored as novel vehicle for the prolonged topical ophthalmic delivery. Gatifloxacin-loaded nanoparticles studied and revealed a fast release during the first hour followed by a more gradual drug release during a 24h period by a non-Fickian diffusion process **[15]**.

Polymethylmethacrylate [PMMA] nanoparticles

Polymethylmethacrylate [PMMA] nanoparticles are made up of in situ emulsion polymerisation technique. Briefly, monomeric methylmethacrylate is dissolved in water or phosphate–buffered saline or a solution or suspension of drugs or antigens in a concentration range of 0.1–1.5% **[16].** Nanoparticles made of 66polyacrylamide or PMMA do not degrade either biologically or enzymatically, which makes them less attractive for topical nanodispersion, but act as good drug delivery carrier as for contact lenses and hydrogels.

Cellulose acetate phthalate Nanoparticles

Cellulose acetate phthalate has been used for in situ gelling of latex nanoparticles **[17]**. The preparation of these latex particles involves emulsification of polymer followed by solvent evaporation. This latex suspension, upon coming in contact with the lacrimal fluid at pH 7.2–7.4, gets converted to gel form in situ, thus increasing the residence time of instilled solution in the eye. But such system is associated with blurring of vision as a disadvantage.

PACA [polyacryl-cyanoacrylate] Nanoparticles

PACA [polyacryl-cyanoacrylate] particles possess properties of biodegradation and bioadhesion that makes them interesting drug carriers for controlled ocular drug delivery and drug targeting. **Wood *et al*** showed that PACA nanoparticles were able to adhere to the corneal and conjunctival surfaces, due to the ability to entangle in the mucin matrix and form a noncovalent or ionic bond with the mucin layer of the conjunctiva, which represent their mucoadhesion property **[11]**. Polyalkylcyanoacrylate [PACA] nanoparticles and nanocapsules have been shown to improve and prolong the corneal penetration of hydrophilic and lipophilic drugs like Betaxolol and amikacin sulfate. Despite these attractive results, the potential of the PACA nanoparticles is limited due to the disruption to the corneal epithelium cell membrane **[18]**.

Poly caprolactone [PECL] nanoparticle/ nanocapsules

Poly caprolactone [PECL] nanocapsules may serve as superior polymer systems for ocular drug delivery due to its biodegradable and biocompatible nature. **Marchal-Heussler *et al*** successfully demonstrated with infusion of compared nanoparticles prepared by using PACA, PECL nanoparticles **[19]**. It was shown that the PECL nanoparticles yielded the highest pharmacological effect. This was believed to be due to the agglomeration of these nanoparticles in the conjunctival sac. Nanocapsules of PECL were also tried for the topical ocular delivery of cyclosporin A [CYA]. It was found that poly-∈-caprolactone coating increased the corneal levels of the drug by 5 times compared to the oily solution of the drug when administered to the cul-de-sac of fully awake New Zealand white rabbits **[12]**.

Eudragitt® nanoparticle

Eudragit® polymer nanoparticle suspensions have been investigated as a carrier system for the ophthalmic release of nonsteroidal antiinflammatory drugs, such as ibuprofen and flurbiprofen **[20].** These inert resins based particles are proposed as delivery systems to prolong the release and improve ocular availability of the drug. They are reported to be devoid of any irritant effect on cornea, iris, and conjunctiva and thus appear to be a suitable inert carrier for ophthalmic drug delivery.

Polybutylcyanoacrylate nanoparticle

Polybutylcyanoacrylate [PBCA] nanoparticle delivery system for pilocarpine nitrate has been evaluated in comparison to the solution of the drug for pharmacokinetic and pharmacodynamic aspects **[18,21,22],** successfully demonstrated the effect of pilocarpine loaded polybutylcyanoacrylate nanoparticles on evaluated aqueous humor drug levels and the intraocular pressure-lowering effects using three models [the water-loading model, the alpha-chymotrypsin model, and the betamethasone model] in rabbits. The miotic response was enhanced by about 33% while the miotic time increased from 180 to 240 minutes for nanoparticles compared to the control solution. Acyclovir-loaded PEG-coated polyethyl-2-cyanoacrylate [PECA] nanospheres prepared by

emulsion polymerization technique showed increased drug levels in the aqueous humor compared to the free drug suspension in the rabbits **[23]**

PLGA Nanoparticles

Polylactide and polylactide-co-glycolide biopolymers in the molecular weight range of 3000–109,000 have been employed in the preparation of nanoparticulate systems for intravitreal administration of acyclovir **[24]**. PLGA is a biodegradable and biocompatible polymer that is hydrolytically degraded into non-toxic oligomer and monomer, lactic acid and glycolic acid **[25]**.

Non-polymeric nanoparticles

Chen et al. developed a new system for local delivery of methazolamide to eye based on calcium phosphate [CaP] nanoparticles. The methazolamide loaded CaP nanoparticles were prepared through the formation of an iorganic core of CaP and further adsorption of the methazolamide. In vitro release studies demonstrated diffusion-controlled release of methazolamide from the CaP nanoparticles over a period of 4 hr. In in vivo studies, it was indicated that the intraocular pressure [IOP] lowering effect of the inorganic nanoparticles eye drops lasted for 18 h, which was significantly better than the effect of 1% brinzolamide eye drops [6 h] **[26,27]**,

Microemulsion/Nanosuspension [MS/NS]

Nanoemulsions are defined as the dispersions of water and oil in the presence of combination of surfactant and co-surfactant [Smix] in a manner to reduce interfacial tension. On the basis of nature of dispersion and disperse phase, NEs were classified as: o/w, w/o & bicontinuous type**.** These systems are usually characterized by clear appearance, higher thermodynamic stability, small droplet size [< 200 nm], high drug solubility, drug reservoir for lipophilic and hydrophilic drugs.

Liposomes

Liposomes are the microscopic vesicles composed of one or more concentric lipid bilayers, separated by water or aqueous buffer compartments with a diameter ranging from 100 nm to 10 μm **[28, 29]**. Liposomes offer advantages over most ophthalmic delivery systems in being completely biodegradable and relatively non-toxic. Another potential advantage of liposomes is their ability to come in an intimate contact with the corneal and conjunctival surfaces, thereby, increasing the probability of ocular drug absorption.

Niosomes

Like liposomes, in recent years, niosomes have been successfully studied for ophthalmic drug delivery as vesicular systems to provide controlled drug delivery, prolonged drug precorneal residence time and enhanced ocular bioavailability and prevention of metabolism of the drug by enzymes present at the tear/corneal surface **[30]**

Dendrimers

As per the definition given by **Sahoo *et al***., "Dendrimers are macromolecular compounds made up of a series of branches around a central core". Their nanosize, ease of preparation, functionalization and possibility to attach multiple surface groups render them suitable alternative vehicle for ophthalmic drug delivery" **[31, 32, 33]**

Solid lipid nanoparticles [SLN]

Solid lipid nanoparticles [SLN] are characteristically spherical particles with an average diameter between 50 to 100nm **[34]**. SLNs are particularly advantageous in ocular drug delivery as they have the ability to enhance the ocular bioavailability of both hydrophilic and lipophilic drugs. Furthermore, they can be easily autoclaved for sterilization which is an important aspect of ocular administration for drug formulation **[35]**.

Table 1: List of different nano-carriers explored by different investigator as possible topical ocular drug delivery carrier

Polymers / Bases/Surfactants based nano–carriers	*Drug Encapsulated*	*Achievement*	*References*
Niosomes – Modification of corneal permeability			
Tween 60/ Brij 35/Tween 80	*Gentamicin*	*Controlled release, Enhanced*	*36*

		corneal deposition .	
Span 60/ Cholesterol/ Chitosan	*Timolol maleate*	*Controlled release, Enhanced permeation*	*37*
Span 40/ Span 60/ Cholesterol	*Acetazolamide*	*Enhanced permeation*	*38*
Sorbitan esters and poly-oxyethylene alkyl ethers	*Naltrexone Hydrochloride*	*Thermoresponsive transition change and increased cornealpermeation*	*39*
Nanosuspensions – Endocytosis and modification of corneal permeability			
Eudragit RS 100	*Ibuprofen*	*Controlled release*	*20*
Eudragit RS 100R/ RL 100R	*Flurbiprofen*	*Controlled release*	*20.*
Eudragit RS 100R/ RL 100	*Cloricromene*	*Improved bioavailability*	*40*
PLGA/Poly[Lac[Glc-Leu]]	*Diclofenac*	*Extended release*	*41*
Pluronic F127	*Timolol*	*High drug loading*	*42*
Sorbitan mono laurate oleate Polyoxyethylenesorbitan monooleate	*Pilocarpine*	*Increased ocular retention*	*43*
Liposomes- modification of corneal permeability			
Phosphatidyl choline / cholesterol	*Puerarin*	*Increased ocular retention*	*44*
Phosphatidyl choline / cholesterol	*Gatifloxacin*	*Improved bioavailability*	*45*
Chitosan/β-glycerophosphate	*Ofloxacin*	*Improved bioavailability*	*46*
Phosphatidylcholine/ cholesterol	*Acetazolamide*	*Increased ocular retention*	*47*
Phosphatidylcholine/ cholesterol	*Ganciclovir*	*Enhanced permeation*	*48*
Dipalmitoylphosphatidyl choline / Cholesterol/Dimethyl-dioctadecyl glycerol bromide	*Acyclovir*	*Enhanced permeation*	*49*
Phosphatidylcholine/ cholesterol	*Ciprofloxacin*	*Improved bioavailability*	*45*
Submicron-sized liposomes	*Edaravone*	*Inhibition of in vitro light-induced reactive oxygen species [ROS] production*	*50*
Chitosan coated liposomes	*Cyclosporin A*	*Prolonged drug retention, enhanced drug permeation, and biocompatibility.*	*51*
Chitosan coated liposomes	*Ciprofloxacin HCl*	*Improved ocular permeation*	*52*
N-trimethyl chitosan [TMC]-coated liposomes	*Coenzyme Q[10]*	*Enhanced permeation*	*53*
Phospholipids and cholesterol	*Tacrolimus*	*Highly effective in suppressing the process of autoimmune uveoretinitis*	*54*
Cationic and anionic surfactants	*Calcein dye*	*Increases the permeability*	*55*
L-α-phosphatidylcholine,Cholesterol,Stearylamineand dicetyl phosphate	*Ciprofloxacin hydrochloride*	*Improved the ocular bioavailability*	*36*
Dendrimers – Diffuses through paracellular pathway			

Poly[amidoamine] [PAMAM]	*Pilocarpine nitrate*	*Increased ocular retention*	*56*
Poly [amidoamine] [PAMAM]	*Tropicamide*	*Increased ocular retention*	*56*
anionic PANAM	*D[+]-glucosamine and D[+]-glucosamine 6-sulfate*	*Synergistic immunomodulatory and antiangiogenic*	*57*
PANAM	*anti-VEGF ODN*	*better mechanical and adhesion ability*	*58*
Polyester [PLGA, PLA] NPs –Endocytosis			
PLGA	*Sparfloxacin*	*Increased ocular retention*	*25*
PLGA	*Methyl trypsin*	*Controlled release*	*59*
PLGA	*Flurbiprofen*	*Enhanced penetration*	*60*
PLGA	*Dexametha zone*	*Sustained release*	*61*
PLGA	*Chloramphenicol*	*Prolonged release*	*62*
PLA	*Betamethasone*	*Targeting specific lesion; controlled release*	*63*
PBCA NPs - Transcellular pathway or endocytosis			
PBCA	*Cyclo-phosphamide*	*Prolonged release*	*64*
PBCA	*Pilocarpine*	*Prolonged release*	*65*
Poly-ε-caprolactone NPs - Transcellular pathway or endocytosis			
PECL	*Indomethacin*	*Increased penetration*	*12*
PECL	*Carteolol*	*Pronounced decrease in IOP*	*66*
Eudragit NPs – Endocytosis			
Eudragit RL 100	*Amphotericin B*	*Controlled release*	*67*
Eudragit RS 100	*Piroxicam*	*Improved ocular delivery*	*68*
Chitosan NPs – Paracellular pathway			
Chitosan	*BSA/ Fluorescein*	*Good toleration*	*69*
Chitosan	*Indomethacin*	*Controlled release*	*70*
Chitosan	*Cyclosporine A*	*Increased bioavailability*	*71*
Albumin NPs – Phagocytosis			
Albumin	*Ganciclovir*	*Prolonged residence in eye*	*72*
Albumin	*Pilocarpine*	*Prolonged residence in eye*	*21*
Albumin	*Aspirin*	*Prolonged residence in eye*	*73*
Albumin	*Hydrocortisone*	*Targeting precorneal area*	*21*

Gelatin NPs			
Gelatin	*Pilocarpine*	*High encapsulation*	*57*
Gelatin	*Hydrocortisone*	*Sustained release*	*57*
PEG NPs – Phagocytosis			
PEG	*Tamoxifen*	*Localization of NPs*	*74*
Modified NPs			
Eudragit RS 100/ RL 100/ PLGA	*Ciprofloxacin*	*Prolonged drug release*	*75*
Eudragit RS 100/ RL 100/ hyaluronic acid	*Gatifloxacin, prednisolone*	*Prolonged drug release*	*76*
Chitosan/ alginate	*Carboplatin*	*Sustained release*	*77*
Chitosan/ hyaluronic acid	*Dorzolamide*	*Reduction in IOP level*	*78*
Chitosan/ sodium alginate	*Gatifloxacin*	*Prolonged drug delivery*	*15*
PLA/ PEG	*Acyclovir*	*Effective*	*79*
Deacetylated water-soluble chitosan	*Flurbiprofen*	*Transcorneal penetration and precorneal retention*	*80*
Chitosan/ poly [D, L-lactic acid] [PLA]	*5-fluorouracil*	*Non-irritant, Diffusion controlled release, Improved bioavailability*	*81*
Chitosan Oligosaccharides [COS]-coated NLC [nanostructured lipid carrier]	*Flurbiprofen*	*Enhanced transcorneal penetration*	*82*
poly- epsilon -caprolactone [PECL],chitosan [CS]-coated PECL,poly[ethyleneglycol][PEG]-coated PECL nanocapsules.	*Fluorescent dye [rhodamine]*	*Improved biodistribution in eye*	*83*
Solid Lipid Nanoparticle			
Stearicacid,Compritol [SLN-B] and poloxamer-188	*Gatifloxacin*	*Physiologically tolerable*	*84*
GMS/ Stearic acid	*Methazolamide*	*Prolonged effect, better patient compliance*	*85*
GMS/ poloxamer	*Baicalin*	*Enhanced ocular bioavailability*	*86*
Phospholipid	*Timolol hydrogen maleate*	*Sustained permeation*	*87*
Dynasan 116	*Cyclosporine A*	*Increased residence time*	*88*
Hexadecyl phosphate	*Tobramycin*	*Improved Bioavailability*	*89*
Glyceryl monostearate/ Poloxamer 188	*Chloramphenicol*	*Improved drug entrapment efficiency and controlled drug release*	*90*
Homolipid/ Phospholipid	*Diclofenac sodium*	*Improved permeation*	*91*

CURRENT CONCEPT

From last 20 years, efforts have been directed in the rational design of ocular drug delivery consisting of mucoadhesive nano-carriers. Thereafter, the plan was directed to generate nanocarriers with a hydrophilic coating with the idea of improving their stability and their interaction with the mucosa **[92, 93, 83, 94]**.

It was proficient via optimization of nanocarriers ocular drug delivery to obtain long-lasting bioadhesion/residence time by the so-called 'mucoadhesive property' based on entrapment of particles in the ocular mucus layer and interaction of bioadhesive polymer chains with mucins **[95]**. Maintenance of the designed nanocarriers in the ocular delivery following topical application is thus decisive to accomplish unremitting drug release and prolonged therapeutic activity. Therefore, manufacture of nanocarriers from mucoadhesive materials is crucial for effective retention in ocular cul-de-sac **[95]**.

Ocular mucoadhesion, exclusively, refers to the capability of certain polymers to hold on to the mucus layer casing the conjunctival and corneal surfaces of the eye by non-covalent bonds. Washout time of mucoadhesive polymeric system is reduced, since this depends on mucous turnover rate rather than lachrymal discharge turnover rate. Mucoadhesive polymer with plentiful hydrophilic functional group *viz* sulphate, hydroxyl, carboxyl, amide have found fundamental role in ocular drug delivery system owing to their adhesion property with precorneal/conjunctival mucin layer via non-covalent bonds, and remaining in place for as long as the mucin is available there. Using this concept, various investigators planned the cationic polymer Chitosan as a polymer of choice because of its unique properties, including good enough biodegradability and biocompatibility **[96, 97, 15, 93, 98]**. Furthermore, it was found that, CH increases cell permeability by affecting both paracellular and intracellular pathways of epithelial cells in a reversible manner without affecting cell viability or causing membrane wounds **[96, 97, 15, 93, 98]**.

During the selection of bioadhesive polymer intended for ophthalmic drug delivery, the viscosity and wetting properties of polymer are considered. Viscosity measures the resistance to flow which depends upon its molecular mass, concentration, temperature and shear stress. In Newtonian system, above a certain range of viscosity there is no real improvement of bioavailability and no further increase of residence contact time and blinking becomes a panic **[99,100,101]**.

On the other hand, polymer showing non-Newtonian behaviour, when incorporated in formulation possessing pseudoplastic behaviour in which viscosity decreases with increasing shear rate [due to blinking and ocular movement], this results in significantly less resistance to blinking and demonstrates greater acceptance as compared to formulation possessing polymer exhibiting Newtonian flow **[101,102]**. The mucoadhesive properties of polyacrylic acid hydrogels and their ability to penetrate the mucin at the surface of the eye have been investigated extensively **[103,104,105,106]**. In the mean time, several other synthetic polymers have been examined for the fabrication of mucoadhesive nanocarriers for ocular delivery, for example Pignatello *et al* reported the formulation and evaluation of nanocarriers composed of Eudragit-RL100 with good ocular tolerance, and no inflammation or discomfort in the rabbit eye **[20]**. According to **[75]**.positively charged nanoparticles could also be prepared when Eudragit RL100 was combined with PLGA.

Barbault-Foucher S et.al reported the Hyaluronic acid [HA] as a natural, nonirritating polysaccharide showing pseudoplastic behaviour with desirable ocular mucoadhesive properties. This group designed the novel ocular drug delivery system based on biodegradable nanospheres coated with a mucooadhesive polymer. The system was composed of a core of poly-e-caprolactone coated by corona of the bioadhesive HA molecule. In this investigation, this group proposed the non-covalent attachment of unmodified HA to the exterior of the nanoparticles. They use three approaches *viz*, i] coating the poly-e-caprolactone core during particle formation by chain entanglement with HA; ii] coating of preformed poly-e-caprolactone nanosystems by HA adsorption; and iii] coating of poly-e-caprolactone nanosystem by electrostatic interactions between negatively charged HA and a cationic surfactant used in the formulation [i.e., a cationic lipid, stearylamine, and a preservative usually used in ophthalmic formulation and absorption enhancer, benzalkonium chloride. The

results made known that HA was robustly attached to nanospheres that had been conferred with a positive charge by cationic surfactant, resulting in intact HA-coated nanospheres. However, like chitosan it does not possess permeability-enhancing properties **[108]**; in addition, the toxicity of stearylamine must be taken into consideration **[95]**. Investigator reported the use of gelatin nanoparticle based on its biocompatibility and biodegradability, since it was derived from the collagen obtained from stroma of the eye, and has been used in extensively in the ocular drug delivery **[109,110,111]**. Tailoring of nano-systems with positive surface functionalization was extensively explored in the recent research trend of ocular delivery technology. [**112]** reported the synthesis and evaluation of positively charged phospholipids and cholesterols as components for liposomes. This group reported that some liposome preparations containing these synthetic lipid materials were found to be non-cytotoxic. Further, they observe that insertion of the positively charged lipid derivatives into the liposomes appreciably improved the ocular withholding compared with neutral or negatively charged liposomes in an un-anaesthetized rabbit eye model, due to molecular association with polyanionic corneal and conjunctival surface mucoglycoproteins. The positively charged functionalized nano-ophthalmic carriers more particularly chitosan imparted positive charged nanosystems investigated in recent time is summarized in **Table 2.**

Table 2: List of mucoadhesive nano-systems investigated in recent years for enhanced ocular retention and bioavailability of drugs

Mucoadhesive Nano-system	***Therapeutic Drug/Biomolecule***	***Transport Mechanism***	***Efficacy***	***Reference***
Chitosan nanoemulsions [nanocapsules]	*Indomethacin*	*Endocytic, Transcellular.*	*Significant increase in drug availability in cornea and aqueous humour.*	***70***
Chitosan coated PECL nanocapsules	*Indomethacin*	*Interaction with corneal surface due to positive charge, transcellular pathway.*	*Significant increase in drug availability in cornea and aqueous humour.*	***113***
Chitosan nanoparticles	*Cyclosporin A*	*Improved interaction with the cornea and conjunctiva, transcellular pathway, specific affinity for some conjunctival cell.*	*significant increase in the CYA concentration in the cornea.*	***83***
	proteins	*Active transport, temperature dependent endocytosis.*	*Increased concentration in ocular tissue.*	***69***
	pDNA		*expression of the encoded protein upon their incubation with corneal and conjunctival epithelial cells.*	***114***
Chitosan coated PLA nanoparticles	*Rapamycin*	*Effective interaction with ocular mucosa*	*Significant increase in allograft survival.*	***115***

Self-assembled Chitosan nanoparticles	*Prednisolone*	*Transcellular pathway.*	*Uniform distribution and improved retention on ocular surface,increase in concentration in aqueous humour.*	***116***
Chitosan polysaccharide nanoparticles	*pDNA*	*Interact with the HA-receptor CD44, expressed in ocular cell lines.*	*significant protein expression corneal and conjunctival epithelial cells.*	***114***
Chitosan lipid nanoparticles	*Flurbiprofen*	*Transcorneal penetration, endocytosis.*	*Improved Precorneal retention.*	***80***
Chitosan Nanostructured lipid carrier	*Flurbiprofen*	*Transcorneal penetration.*	*Delayed clearance from ocular surface.*	***82***
chitosan-coated liposomes	*Cyclosporin A*	*Transcellular pathway, positive charge interaction with mucin.*	*concentrations increased in cornea, conjunctiva, and sclera.*	***51***
Chitosan Liposomes	*Ciprofloxacin hydrochloride*	*Diffusion.*	*enhanced antimicrobial activity against both Gram-positive and Gram-negative bacteria.*	***52***
N-trimethyl chitosan [TMC]-coated liposomes	*Coenzyme Q[10]*	*Transepithelial transport.*	*elevated the cell viability and reduced the oxidative damage.*	***53***
Chitosan coated niosomes	*Timolol*	*Paracellular pathway, corneal retention.*	*Sustained control of the intraocular pressure.*	***117***

Overall, the promising results illustrated in the literatures point towards the acceptance of nano-technological carry as future nanomedicine for topical ocular administration bioactives. In addition, surface functionalized with positive charge nanomedicine has emerged as an extremely promising candidate, given their improved interaction with the ocular surface and hence, enhanced ocular residence with prolonged delivery of the carried bioactives in ophthalmology.

CONCLUSION

Development of nano- sized novel formulations is worthwhile in such cases of ophthalmic delivery as they are expected to prolong the pre-ocular retention and increase the ocular bioavailability.Drug enclosed in the vesicles and oily nano-droplets allows for an improved partitioning and transport through the cornea. Moreover, vesicles offer a promising avenue to fulfil the need for an ophthalmic drug delivery system that has the convenience of a drop, but will localize and maintain drug activity at its site of action **[118, 31].** Finalythis review conclude that nano sized formulation, [nanoemulsion, niosome, etc.,] were achieved higher inner ocular tension and minimize systemic drug absorption. Hence we proposed novel nano sized formulation were suitable for prolonged delivery of drug in ophthalmology.

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