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Recent Drug Delivery Systems for Treatment of Glaucoma

Noha S El-Salamounia[1]* and Ragwa M Farida[1]

[1]Department of Pharmaceutics, Faculty of Pharmacy & Drug Manufacturing, Pharos University in Alexandria, Egypt

*Corresponding author: Noha S El-Salamouni, Faculty of Pharmacy and Drug Manufacturing, Pharos University in Alexandria, Alexandria, Egypt, Tel: +20100-60-20-345/+203-3877111; Fax: +2 03 3830249; Email: noha.soliman@pua.edu.eg

ABSTRACT

Elevated Intraocular Pressure **(IOP)** is the most important risk factor for the development of glaucoma, its reduction is achieved mostly by topical administration of anti-glaucoma drugs as eye drops. A major problem that reduces the clinical efficacy of these drugs is the attainment of an optimal drug concentration at the site of action. To achieve effective ocular hypotensive effect, an adequate amount of the drug should be delivered to the eye and maintained in the ocular tissues for a prolonged period of time.

Recently, several drug delivery systems were designed to enhance corneal residence time and ensure consistent IOP reduction. These delivery systems include; ocular inserts, contact lenses, *in-situ* hydrogels in addition to, colloidal carriers as liposomes, lipid nanoparticles, niosomes and polymeric nanoparticles. These delivery systems aim at increasing the ocular bioavailability and clinical efficacy of anti-glaucoma drugs and proved to be advantageous compared to eye drops. This chapter will focus on the recent emerging drug delivery systems for treatment of glaucoma.

Keywords: Glaucoma; Inserts; Contact lenses; Nanoparticles; Liposomes; Nanostructured lipid carriers; Intraocular pressure

Abbreviation: IOP : Intraocular pressure ; CLs : Contact lenses; HPMC : Hydroxypropyl methyl cellulose; SA : Sodium alginate; SLNs : Solid lipid Nanoparticles; NLCs : Nanostructured lipid carrier;

INTRODUCTION

Conventional first-line therapy for glaucoma involves applying one or more topical eye drops designed to lower IOP by at least 25%, accounting for individual patient risk factors and severity of the disease [1]. Contact time of the topically applied drugs with the eye surface is limited due to continuous secretion of tear fluid; this in turn reduces their ocular bioavailability [2]. Therefore, less than 5% of a topically applied drug is absorbed through the cornea into the eye [3]. Other disadvantages of topically used eye drops include limited capacity of conjunctival cul-de-sac, problematic treatment schedules, and difficulty in application of eye drops. In addition, drainage into the nasolacrimal duct, binding to melatonin or proteins and metabolism within the ocular tissues [4]. Various adverse effects associated with topical medication may have a negative effect on patient adherence to medical treatment, doctor-patient relationship and patient quality of life [5]. In an effort to improve treatment efficacy and clinical outcomes, recent research has concentrated on developing novel systems for achieving sustained drug delivery in glaucoma.

One strategy for achieving sustained delivery of glaucoma drugs; creating novel delivery systems to increase the precorneal residence time of the drug. Moreover, creating a more permanent reservoir of the drug on or near the cornea aiming to increase its bioavailability and minimizing unwanted systemic side effects [1].

Different strategies have been developed to increase the bioavailability of ophthalmic drugs by prolonging the contact time between the ophthalmic formulation and the ocular tissues. The following strategies have been used to improve the ocular bioavailability: (i) improvement of corneal permeability by chemical and pharmaceutical modification (e.g. pro-drugs, penetration enhancers, ion pairs, iontophoresis and cyclodextrins); (ii) improvement of retention by vehicle (e.g. suspensions and ointments, viscous vehicles, bioadhesive vehicles and *In-situ* gelling systems); (iii) improvement of retention by colloidal dispersion systems (e.g. liposomes, emulsions, nanoparticles and nanocapsules); (iv) improvement of retention by solid polymeric matrix and devices (e.g. degradable matrices, non- degradable matrices, collagen shields and contact lenses, and membrane-controlled devices); and (v) implantable devices [6,7].

OPHTHALMIC INSERTS

Inserts, sheets and films could be interchangeable. They are defined as sterile preparations, with a thin, multilayered, drug-impregnated, solid or semisolid devices of appropriate size and shape designed to be placed in the conjunctival sac (between the lower eyelid and the eye itself)

[8]. These devices are designed to release the drug at a constant rate for a prolonged time while minimizing systemic absorption and improving patient compliance due to a reduced frequency of administration. Advantages of these solid devices allow accurate dose delivery, avoid the use of preservatives, and can notably increase ocular bioavailability. While their drawback is the foreign body sensation accompanied with its initial administration as well as the potential for movement or expulsion [9].

CONTACT LENSES

Contact Lenses **(CLs)** consist of curved plastic disks, which cling to the corneal tear film due to their surface tension. Contact lenses are attractive for ocular drug delivery systems as significantly prolong the residence time of the drug in the eye, high degree of comfort which improve patient compliance, higher efficiency and low side effects and, hence increase the ocular drug bioavailability. Also CLs reduce the need for the addition of permeation enhancers and preservatives commonly used in multi dose eye drops, which may cause ocular irritation [10]. Their mechanism of action includes drug diffusion into the post-lens tear film followed by dispersion in the tear fluid and subsequent absorption by the cornea. Due to the constant absorption of the drug through the cornea, the concentration of the post-lens tear fluid remains lower than its concentration in the CLs, creating a constant and prolonged drug flow from the CLs to the cornea [11]. This is called the *sink effect* [12]. This method results in an increased retention of the drug on the surface of the cornea (about 30 min) as opposed to around 2 min for eye drops [13] and a bioavailability equal to or greater than 50% [14].

Basically two approaches have been used to incorporate drugs into contact lenses; loading drugs into preformed lenses, or manufacturing the lens with the drugs entrapped inside. Attempts were also made by dissolving drug in the monomer solution and followed polymerization, incorporation of drug loaded nano or micro based vesicular systems into the matrix. In addition to molecular imprinting, particle-laden soft contact lenses, barrier approach, and complexation [15] (Table 1).

Drug delivery system	Carrier composition	Drug	Major Outcomes	Ref.
Inserts, sheets and films				
Nano-fiber patches	Polyvinyl alcohol Polycaprlactone	Timolol maleate Dorzolamide hydrochloride	The developed formulation possesses very high mucoadhesive strength, thus can be retained for a longer period in the eyes. Moreover, the formulation was capable of maintaining the IOP for up to 72 h.	[16]
Nano sheet	Chitosan Sodium alginate **(SA)**	Latanoprost	Nanosheet containing latanoprost (2.5mg/cm) was sustained for 7 days without any evidence of local adverse effects and revealed IOP reduction of more than 20% in rats	[17]
Film	Chitosan	Timolol maleate	Drug was released over 4 weeks, (85% released over the first 2 weeks). However, the film's release of drug lowered *in-vivo* IOP levels over 10 weeks. No significant difference was observed in IOP reduction in rabbits treated with 0.5% commercial ophthalmic solution, compared to those receiving the films ($P<0.05$). No signs of ocular discomfort or irritation were identified.	[18]
Inserts	PVP K-90, Hydroxypropyl methycellulose **(HPMC)** Carbopol SA Chitosan	Brimonidine	Ocular inserts composed of 7% PVP, 1.5% SA with or without ethylcellulose coat was able to sustain the *in-vitro* release of brimonidine (99% at 6h). Their therapeutic efficacy regarding IOP lowering effect when inserted in albino rabbits eyes showed superior sustainment effect compared with that of brimonidine solution. The one-side-coated ocular insert showed more IOP lowering effect compared with that of its non-coated or dual-side-coated counterpart.	[19]
Inserts	HPMC SA Sodium carboxymethyl cellulose	Brimonidine tartrate	Inserts based on NaCMC were superior over other inserts with respect to swelling, bioadhesion and extended release. All inserts showed a significant IOP lowering in normotensive rabbits. SA based inserts showed a stable IOP lowering effect for 5h.	[20]
Contact lenses				
Contact lenses	Senofilcon A **(ACUVUE®)**	Dorzolamide Timolol maleate	The lenses loaded with both drugs exhibited superior IOP reduction compared to eye drops with about 6-fold lower drug loading. In addition, Vitamin E incorporation was highly effective in increasing the release durations of both drugs to about 2-days.	[21]
Contact lenses	Senofilcon A **(ACUVUE®)**	Latanoprost	The *in-vivo* animal study showed that contact lenses containing polymer-drug (latanoprost) films 40-45mm in thickness provided an initial burst of latanoprost in the aqueous humour followed by a steady-state concentration comparable with the average hourly concentration delivered from a drop of commercially available latanoprost.	[22]
Contact lenses	Propoxylated glyceryl triacylate **(PGT)** nanoparticles in CL	Timolol maleate	Preliminary animal studies in Beagle dogs conducted with lenses in which PGT nanoparticles loaded with timolol and incorporated into hydrogel contact lenses show steady drug delivery over a month after an initial burst and a reduction in IOP.	[23]
Contact lenses	ACUVUE® TruEye™ (Narafilcon A)	Timolol maleate	The *in-vivo* studies showed that IOP reduction from baseline by pure contact lens on daily basis was comparable with that by eye drops but with only 20% of drug dose, which suggested higher drug bioavailability for contact lenses. In addition, by inclusion of vitamin E into the lenses, the IOP was reduced significantly during the 4-day treatment with continuous wear of lens.	[24]
Contact lenses	ACUVUE® TruEye™ (Narafilcon A)	Timolol maleate	Lenses with one-third of the drug loading as conventional eye drops resulted in similar IOP reduction, suggesting higher bioavailability for contact lenses compared to eye drops. Inclusion of vitamin E into the lenses did not improve the IOP reduction.	[25]
Contact lenses	Poly(2-hydroxy-ethyl methacrylate) **(pHEMA)**	Acetazolamide Ethoxolamide	Biomimetic networks can load more drug and control better drug release than conventionally synthesized pHEMA hydrogels. The biomimetic hydrogels were highly cytocompatible and possessed adequate oxygen permeability to be used as medicated soft contact lenses or inserts	[26]
Contact lenses	Poly(2-hydroxy-ethyl methacrylate-co-N vinylpyrrolidone-co-methyl acrylate) **(pHEMA-NVP-MA)**	Puerarin	In rabbit eyes, the presoaked contact lenses extended the mean resident time of puerarin to 77.45 min from 12.88 min of 1% puerarin eye drops. Moreover, contact lens presoaked in puerarin solution at the concentration of 0.802 mg/ml showed about the same bioavailability (AUC_{0-F}) in tear fluid as that of the puerarin eye drops. This type of presoaked contact lens has potential application as vehicle of puerarin to alleviate glaucoma.	[27]

IN-SITU HYDROGELS

In-situ gel-forming ophthalmic drug delivery systems prepared from polymers that exhibit reversible phase transitions (sol-gel) and pseudoplastic behavior to minimize interference with blinking [28]. *In-situ* gel forming polymeric formulations offer several advantages, such as sustained and prolonging the contact time between the drug, and the corneal and/or conjunctival epithelium [29] due to enhanced viscosity and mucoadhesive properties [30]. In addition, from a manufacturing point of view, the production of such devices is less complex and, thus, lowers the investment and manufacturing costs [30]. The phase transition of the *in-situ* gelling systems on the eye surface can have different causes, including: temperature and pH in the precorneal region or the electrolyte composition of the tear film [7,31,32]. Since the resulted swollen hydrogel is aqueous based, it is very comfortable in the human eye. *In-situ* gels are preferred since they are conveniently dropped in the eye as a solution, where undergo transition into a gel [33].

Cheng *et al* [34] concluded that after topical application of latanoprost-loaded chitosan based hydrogel, in triamcinolone acetonide-induced elevated IOP in rabbit eyes was significantly decreased within 7 days and remained at a normal level for the following 21 days. This newly developed chitosan-based hydrogel may provide a non-invasive alternative to traditional anti-glaucoma eye drops for glaucoma treatment.

Avinash and Ajay [35] concluded that the developed thermo reversible *in-situ* gel formulation containing Clonidine Hydrochloride drug and polymer ratio in 17% Polaxmer 407 with 0.45% HPMC exhibited best evaluation parameters regarding viscosity and mucoadhesivness.

Geethalakshmi and co-authors [29] study supports that the Pluronic/HPMC based *in-situ* gel vehicle showed excellent ocular tolerance and exhibited controlled drug release for Betaxolol hydrochloride which could exhibits a greater potential for glaucoma therapy.

Gupta and Vyas [36] developed an *in-situ* gelling system composed of Carbopol W 940 (0.4%, w/w) and Chitosan (0.5%, w/w) with Timolol maleate. This formulation underwent rapid transition into the viscous gel phase at the pH of the tear fluid (pH 7.4) and prolonged the residence time of TM in the cul-de-sac increasing its bioavailability compared with a commercial TM solution. Thus the developed system is a viable alternative to conventional eye drops

Gupta *et al* [37] study showed that the *in-vivo* studies on dexamethasone-induced glaucomatous rabbits indicated that the IOP lowering efficacy for forskolin nanosuspension in polycarbophil (1.0%, w/w)/poloxamer 407 (30%, w/w) hydrogel systems was 31% and lasted for 12 h, which is significantly better than the effect of traditional eye suspension (18%, 4-6 h).

COLLOIDAL NANOCARRIERS

The use of colloidal nanocarriers provides numerous advantages for ocular drug delivery, due to their ability to protect the entrapped drug while facilitating its transport to different eye

compartments. Moreover, nanocarriers can provide controlled drug delivery for prolonged time periods which is advantageous for the treatment of chronic ocular diseases like glaucoma [38].

Colloidal carriers may be applied as liquid dosage similar to eye drop solutions, which by interaction with the corneal and conjunctival glycoproteins form pre-corneal depot prolonging the drug release [39]. Furthermore, several studies incorporated colloidal carriers in preformed hydrogel of in-situ gelling system to enhance ocular residence time [40-42].

During the last decade, several anti-glaucoma drugs have been incorporated into lipid based carriers. Both liposomes and lipid nanoparticles, showed promising results and enhanced ocular bioavailability.

Liposomes

Liposomes are vesicular carriers composed of one or more concentric phospholipid bilayers enclosing aqueous compartments. The location of drug incorporation in liposomes depends on its physicochemical properties and the lipid type used in the preparation of liposomes [43].

Liposomes offer several advantages as a vehicle for ophthalmic drug delivery [44]. They are easily administered in liquid dosage forms, yielding high patient compliance, however can localize and maintain drug activity at the site of action. Moreover, liposomes prolong and control the drug action at the corneal surface, prevent drug metabolism by the enzymes present at the tear/corneal epithelial surface by the barrier effect of the vesicles [44]. Moreover, liposomes were reported to improve corneal drug absorption of both hydrophilic and lipophilic drugs [43].

The surface charge, lipid composition and bilayer rigidity of the vesicles can alter the behavior of the drug entrapped and its affinity the corneal surface. The surface charge confers high physical stability to liposomal by preventing their fusion and imparting them a high zeta potential [43]. Positively charged vesicles were reported to prolong precorneal retention, increase ocular bioavailability and enhance the pharmacological effect compared to negatively charged and neutral liposomes, due to their strong mucoadhesion and binding to the negatively charged mucin [45]. However, stearyl amine; commonly used to impart a positive surface charge to liposomes was reported to be toxic to cells, and irritant to the eye. On the other hand, neutral liposomes were found to be safe for ophthalmic use [45].

Proliposomes are anhydrous form of concentrated liposomes that are used to prepare liposomes by simple hydration [46]. They are more stable precursors for liposomes that can be reconstituted directly before use [47].

Lipid Nanoparticles

Recently, nanoparticulate carriers have been considered for topical ophthalmic drug delivery by facilitating its transport to different compartments of the eye [48]. They can prolong corneal residence time and improve corneal penetration, due to their lipophilic character, bioadhesive

property, small size and particulate nature. Thus, becoming attractive carrier for treatment of ocular diseases [48,49].

Solid Lipid Nanoparticles **(SLNs)** are advantageous, alternative to traditional colloidal systems, eg; emulsions, liposomes, polymeric microparticles and nanoparticles [50]. SLNs are composed of solid physiological lipids stabilized by non-toxic emulsifiers e.g., poloxamer taurocholates and lecithin permitting repeated administration. They are formulated as liquid dosage forms to be administered as eye drops; incorporating either lipophilic or hydrophilic drugs [51]. The lipid matrix of SLNs is solid both at body and room temperatures and tightly binds the incorporated drug, hence reducing its mobility and allowing controlled drug release, protecting sensitive drugs from degradation compared to conventional colloidal systems [52].

However, after preparation lipids partially crystallize in high energy modifications with many imperfections in the crystal lattice. These modifications can transform into low energy modifications during storage, reducing the imperfections in the crystal lattice and leading to drug expulsion [53].

To overcome this limitation, Nanostructured Lipid Carriers **(NLCs)** were produced, exhibiting excellent features for use as a drug carrier, with improved physical and chemical stability [50]. NLCs are prepared by controlled mixing of solid lipids with spatially incompatible liquid lipids allowing a less crystallized matrix, thus, improves the drug loading and reduces drug expulsion during storage [53]. NLCs remain in the solid state at the body temperature, controlling the drug release [54] (Table 2).

Table 2: Recent studies on lipid based delivery systems for treatment of glaucoma.

Drug delivery system	Carrier composition	Drug	Major outcomes	Ref.
Liposomes				
Unilamellar esicles	Soya phosphatidylcholine Cholesterol	DiltiazemHCl	Vesicles, rigidified using cholesterol in 1:1 molar ratio were the most stable. Cholesterol incorporation increased the % entrapment efficiency and decreased the drug release rate. An enhanced IOP lowering activity in rabbits' eyes, was obtained compared to solution.	[43]
Small unilamellar vesicles	Cholesterol DPPC (1, 2 – Dipalmitoyl-sn-glycero-3-phosphocholine)	Brimonidine tartrate	Liposomes were 210 nm size and drug loading ~ 30 - 40%, with slow and prolonged release of drug, following zero order kinetics. The IOP lowering activity in normotensive rabbits was sustained for longer period of time than drug solution.	[55]
Large unilamellar vesicles	Egg-phosphatidylcholine	Latanoprost	A sustained in-vitro release (60%) was achieved for 14 days. Sub conjunctival injection of liposomes maintained a sustained IOP lowering effect in rabbit eyes (4.8 ± 1.5 mmHg) compared to topical daily latanoprostadministration(2.5 ± 0.9 mmHg) for 90 days without signs of ocular inflammation.	[56]

Liposomal gels	Phospholipon® 90G Cholesterol Pluronic® F127 (gelling agent)	Latanoprost	Latanoprost interacted with excipients in liposomes, resulting in enhanced drug encapsulation, the optimum liposomes were composed of 7:3 lipid:cholesterol ratio and 1:1 drug:lipid ratio and showed ~98% entrapment efficiency. Vesicles incorporation into Pluronic® F127 gel sustained drug release (~45% released in 2 days). Liposomal gels were non-irritant to rabbits' eyes and sustained the IOP reduction for 3 days, compared to Xalatan® eye drops.	[57]
Liposomes	SoyabeanPhosphatidylcholine (S100) Cholesterol	Brinzolamide	Optimal liposomes contained lipid/cholesterol ratio (7:4) and lipid/drug ratio (10:1), showed EE of 98.32 ± 1.61% and a diameter of 84.33 ± 2.02 nm. Liposomes (1mg/ml) showed 6.2 folds increase in the corneal permeability coefficient and a more sustained and effective IOP reduction in rabbit's eyes (5-10 mmHg) compared to commercial suspension (10mg/ml).	[58]
Nanoliposomes	Phospholipon85G® Cholesterol	DorzolamideHCl	Optimum liposomes were composed of phosphatidylcholine: cholesterol in 7:4 ratio, below 100 nm and showed enhanced transcorneal permeation compared to dorzolamide solution and greater IOP lowering activity and a more prolonged effect compared to Biosopt® eye drops.	[59]
Liposome in ion sensitive *in-situ* gel	Soybean Phosphatidylcholine Cholesterol Deacetylatedgellan gum (gelling agent)	Timolol maleate	Optimal liposomes were 136 nm with 47% entrapment efficiency and 1.93 folds enhancement of corneal penetration. Liposomes in *in-situ* gel revealed a corneal retention time superior to commercial eye drops and to liposomes and was non-irritant to ocular tissues and showed fast IOP reduction compared to eye drops.	[60]
Lipid nanoparticles				
SLNs NLCs	Glycerylmonostearate (solid lipid) Castor oil (liquid lipid)	Brimonidine	Both SLNs and NLCs were physically stable following autoclaving at 121°C for 15 min, yielding particles below 500 nm, non-irritant to ocular mucosa, with increased ZP and amount of brimonidine entrapped compared to non-autoclaved ones.	[52]
Cationic SLNs	Softisan® 100 (solid lipid) Stearic acid (lipid modifier)	Melatonin	Didecyldimethylammonium bromide was used as positive charge imparter to produce cationic SLNs, which showed good mucoadhesion, enhanced ocular retention time, good tolerability and was very effective in IOP reduction for 24 h (maximum IOP reduction -7mmHg).	[61]
Surface modified SLNs by chitosan	Glyceryl Monostearate (solid lipid) Lecithin	Methazolamide	Chitosan modified SLNs were superior to non-modified, they exhibited more stable particles (4 months at 4°C), smaller size (199.4 ± 2.8nm) with a prolonged in-vitro release and better corneal permeation. The peak decrease in IOP (42.78 ± 7.71%) was superior to both un-modified SLNs and AZOPT® eye drops, without any signs of ocular irritancy.	[62]
SLNs	Glycerylmonostearate (solid lipid) Phospholipid S100	Methazolamide	SLNs were optimized using Box-Behnken design and exhibited 197.8 ± 4.9 nm size, 68.39% drug entrapped, a sustained release following Peppas model and a significant prolonged IOP reduction compared to AZOPT® without any signs of ocular irritation.	[63]

Cationic nanostructured lipid matrix	Compritol® 888 ATO Cetosteryl alcohol Stearylamine (positive charge imparter)	Methazolamide	The optimized formulation composed of a mixture of heterolipids (cetosteryl alcohol and compritol) in 2:1 ratio, showed 207.1 nm size 25.62% entrapment efficiency and lowered the IOP by 8.3 mm Hg within 3 h and was maintained for 12 h.	[64]

Niosomes

Niosomes are nonionic surfactant-based bilayer vesicles, formed by the self-assembly of nonionic amphiphiles in aqueous medium [65], entrapping either hydrophilic or lipophilic drugs in the aqueous layer or the vesicular membrane [66]. Niosomes offer several advantages over other vesicles as a topical ocular delivery system. They are non-immunogenic, biodegradable, lower in cost, chemically stable and of low toxicity due to their nonionic nature. Moreover, they can improve the drug performance by enhancing its bioavailability and controlling its delivery at a specific site [45,67].

Niosomes of polyoxyethylene alkyl ethers [68], series of Spans and Tweens [69], and ester linked surfactants, Brij [70], were developed to improve ocular drug delivery and were tested in several animal models. Also positively charged niosomes were prepared and showed better precorneal binding and higher bioavailability [71,72]. However, due to problems of physical instability of niosomes during storage, including; vesicles aggregation or fusion and leaking or hydrolysis of encapsulated drugs, niosomes can be entrapped in *in-situ* hydrogel system. This system can increase the precorneal residence time, enhance ocular bioavailability, and reduce the frequency of administration [67].

In a study, the effect of Span type and cholesterol level in timolol maleate-loaded niosomes, were investigated and showed that niosomes based on Span 40 using Span:cholesterol ratio (7:3) revealed an enhanced IOP reduction compared to Span 20 and Span 60 [73]. In another study, small unilamellar niosomes, loaded with dorzolamide hydrochloride were prepared using Span 40:Tween 80 or 40:cholesterol:dicetylphosphatein 75:75:40:10 ratio. Niosomes were nanometric, physically stable and exhibited a prolonged release rate compared to solution, thus was reported as a promising carrier for prolonged IOP reduction [74].

Abu Hashim *et al*, optimized atenolol niosomal hydrogel formulation using Span 60:cholesterol in (2:1) ratio in carbopol 934P. Niosomes exhibited a sustained release and a more pronounced IOP reduction compared to atenolol solution and other polymeric hydrogels [42].

Polymeric Nanoparticles

They are polymeric colloidal particles from 10-1000 nm, in which the drug is dissolved, encapsulated, entrapped or adsorbed to the surface, thus, enhancing drug stabilization [75]. Nanoparticles formed of synthetic polymers e.g. polyamidoamine **(PAMAM)** dendrimers, polyguanidilyateddendrimers, and polybutylcyanoacrylate improved the efficiency of ocular

drug delivery [41]. However, natural bioadhesive polymers e.g. chitosan, SA are superior to synthetic polymers for ophthalmic formulations, due to their nontoxicity, biodegradability and biocompatibility [40] (Table 3).

Table 3: Recent studies on nanoparticles for treatment of glaucoma.

Drug delivery system	Carrier composition	Drug	Major outcomes	Ref.
Polymeric nanoparticles in preformed gel	Chitosan Methyl cellulose (gelling agent)	Brimonidine	Optimized chitosan nanoparticles, incorporated in preformed gel showed sustained release superior to SA nanoparticles due to adhesion to negatively charged cornea and conjunctiva. Cytotoxicity studies revealed non-toxic formulations with sustained IOP reduction (>25h) compared to eye drops.	[40]
In-situ gelling polymeric nanoparticles	Chitosan SA (gelling agent)	Dorzolamide hydrochloride	Optimized nanoparticles (164 nm, 98.1% entrapment efficiency), showed sustained *in-vitro* release and slower corneal permeation (35.5%) compared to commercial eye drops (86.34%). Nanoparticles were mucoadhesive, non-irritant and revealed a long retention in rabbit's eyes.	[41]
Polymeric nanoparticles	Poly (lactide-co-glycolide)	Dorzolamide hydrochloride	Nanoparticles revealed 1.8-2.5 fold enhancement in corneal permeation compared to Trusopt® and higher drug concentration in aqueous humour (1.5-2.3 fold).Vitamin E TPGS as an emulsifier proved to be safer and effective compared to PVA. It acts as a P-glycoprotein inhibitor (prominent efflux transporters on ocular tissues) and caused a significant increase in entrapment efficiency, corneal permeation and sustained IOP reduction.	[76]
Polymeric nanoparticles	6-O-Carboxymethyl chitosan	Dorzolamide hydrochloride	Water soluble 6-O-carboxymethyl chitosan derivative yielded small nanoparticles superior to chitosan in mucoadhesion and by 14% in entrapment efficiency and sustained drug release. *In-vivo* studies revealed non-irritant particles with prolonged anti-glaucoma effect.	[39]
Polymeric nanoparticle	Chitosan	Betaxolol hydrochloride	Optimized nanoparticles composed of (1:2) polymer:drug ratio, exhibited biphasic release pattern with an initial burst followed by sustained release up to 12h. Nanoparticles showed good ocular tolerance and significant IOP reduction reaching peak of 9.9±0.5 mmHg, compared to control after5h.	[77]

CONCLUSION

Topical medications play an important primary and adjunctive role in the treatment of glaucoma. Novel delivery systems could achieve an efficient and targeted anti-glucomatic approach by improving the pre corneal residence time and corneal permeation of the drug. In addition, they have the potential to improve patient adherence, reduce side effects, increase efficacy, and patient quality of life.

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