The emerging potential of Nano-formulations of Timolol Maleate in Glaucoma Management

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Abstract

Ocular diseases are on the high and glaucoma is among the top. Visual impairment, excessive tearing, and irreversible damage to the optic nerve make glaucoma a significant problem. Timolol maleate is a common drug used to lower intraocular pressure due to its androgenic antagonist activity. Currently, Timolol solutions are available for treatment. However, due to various eye barriers such as tear dilution, tear turnover, and nasolacrimal drainage therapeutic efficacy and patient compliance have effectively decreased. Nanoformulation has garnered attentiveness in recent years due to overcoming challenges such as drug stability, solubility and targeted drug delivery offered by novel treatment approaches. Their complex structure, drug encapsulation, ability to overcome ocular barriers and improved bio-availability make them an ideal drug delivery system. A paradigm shift has been observed by emergence of nano formulations of anti-glaucomatic drugs such as liposome, niosomes, cubosomes, nano-fibers particularly a Timolol maleate. This review highlights Timolol maleate nano formulations for optimized therapeutic outcomes. Their type, efficacy in vitro and in vivo along with future prospects are discussed. Continuous exploration of this field for improved management of glaucoma is compelling for eventuality of ocular drug delivery system.

Keywords

Glaucoma, Timolol maleate, Nanoformulation, Targeted drug delivery.

1. INTRODUCTION

Glaucoma is a group of optic neuropathic degenerative diseases that are progressive. Glaucoma affects the optic nerve: it extends from the central nervous system (CNS) and is critical for vision, leading to partial or complete vision loss. Genetic and biological risk factors lead to optic nerve damage (Sharma *et al.*, 2023). In addition, Glaucoma-age-related increases the intraocular pressure in the eye that progressively affects per-

ipheral vision. Left untreated may lead to significant and irreversible vision loss. However, a multi-drug regimen is a way to stop peripheral vision. After cataracts, glaucoma is the subsequent leading cause of blindness, consequently raising major public health concerns (Bourne *et al*., 2018; Cook & Foster, 2012). Enhanced drainage and reduced production of aqueous humor are the treatment goals for glaucoma.

Worldwide, about 60 million people suffer from glaucoma optic neuropathy. In addition to this, almost 8.4 million individuals are visually impaired because of glaucoma(Cook & Foster, 2012) . For people aged 40-80, the worldwide occurrence of glaucoma is 3.45%; for primary open-angle glaucoma (POAG), prevalence is highest in Africa at 4.20%. Primary angle closure glaucoma (PACG) frequency is highest in Asia at 1.09%. In 2013, 63 million individuals were affected by glaucoma, which drastically expanded to 76 million in 2020 and is estimated to hit 111.8 millions by 2040 (Tham *et al*., 2014).

Ciliary muscles in the eye secrete a fluid called aqueous humor (Thau *et al*., 2018). This fluid then follows the path and flows through the pupil between the iris and cornea, leaving the eye from trabecular meshwork located at the base of the iris, functioning as a drain (Clark, Miggans, Wilson, Browder, & McCartney, 1995). A balance between the production and drainage of aqueous humor is evident in normal healthy eyes. This balance is disturbed by the partial or complete blockage of eye trabecular meshwork, resulting in fluid buildup and glaucoma (Thau *et al*., 2018). A significant rise in intraocular pressure caused by blockage in aqueous humor ultimately leads to degeneration of the optic nerve (Gupta & Weinreb, 1997).

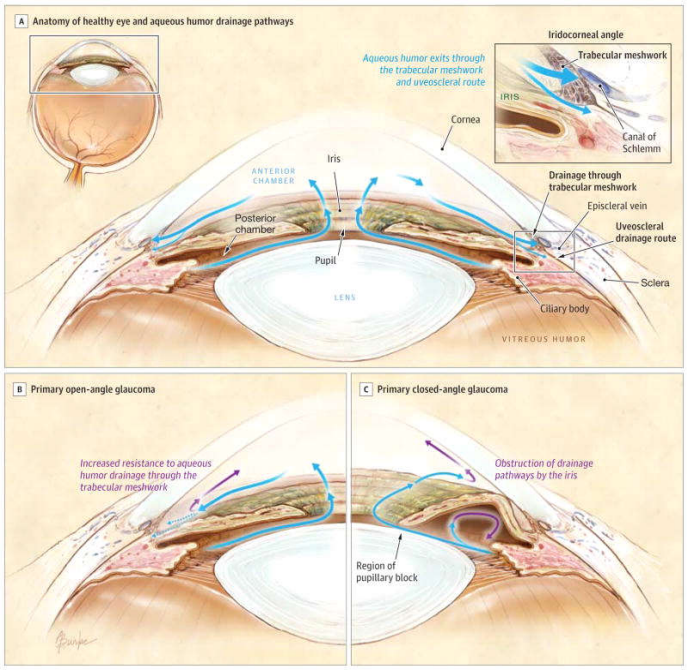

Fig-1: **Anatomy of healthy eye and aqueous humor drainage pathways, (B) Primary open-angle glaucoma, (C) Primary closed-angle glaucoma.(Weinreb, Aung, & Medeiros, 2014)**

Timolol Maleate(TM), S-(“)-1-[(tert-butylamino)-3-(4-morpholino-1,2,5-thiadiazol-3-yl)oxy]-2-propanol maleate is a non selective beta-adrenergic antagonist (Mortazavi, Jafariazar, Ghadjahani, Mahmoodi, & Mehtarpour, 2014). Timolol has long been used to treat glaucoma and is still very much used today since its introduction in late 1978 (Rathore, Nema, & Sisodia, 2010). Timolol is also efficient in treating hypertension, arrhythmias, and angina pectoris, as well as the secondary prevention of myocardial infarction (Turkdemir, Erdögdu, Aydemir, Karagözler, & Karagözler, 2001) . Timolol acts by inhibiting the beta receptors, specifically beta-2 receptors, in the eye's ciliary epithelium, lowering the amount of aqueous humor produced in the eye, lowering intraocular pressure, and thus aiding in the treatment of glaucoma. Currently, timolol is available as an ophthalmic solution at concentrations of 0.5% and 0.25% (Rathore *et al.*, 2010).

Nanoformulations are becoming the new mainstay in ocular drug delivery. Researchers from all around the globe are focusing on using these tiny-sized particles to overcome the challenges of conventional ocular medications (El Hoffy, Abdel Azim, Hathout, Fouly, & Elkheshen, 2021). Similar is the case for anti-glaucoma drugs. A wide range of drug delivery systems like nanocrystals, dendrimers, liposomes, lipid-based nanocarriers, polymeric nanoparticles, and nano emulsions are currently under research. Timolol has emerged as a drug of interest owing to its enhanced penetrability, controlled drug delivery and improved therapeutic effect in nano size. Moreover, nanosized timolol maleate offers little to no irritation to the eye (Ikuta *et al*., 2017). Without eye irritation, the tear turnover and rapid blinking on drug instillation decreases. This reduction favors the drug residence time, increasing drug absorption. (M. Singh, Bharadwaj, Lee, & Kang, 2020).

In this review, we focus on the emerging nanoformulations of timolol maleate as an anti-glaucoma drug by discussing the various drug delivery systems, their preparation, potential and future prospects.

2. Literature review:

2.1. Niosomes

Niosomes have been employed to address the issue of drug insolubility, instability, and rapid degradation (Chen, Hanning, Falconer, Locke, & Wen, 2019). It offers specific carriers, novel methods of transfer and release of drugs, prolonging therapeutic effectiveness and facilitating intracellular delivery. Furthermore, it is feasible to protect the drug from deterioration during storage and in in-vivo circulation. The majority of niosomes are made up mostly of non-ionic surfactants and additives. Cholesterol is the additive and bio-adhesive in noisome and the vesicular layer is the name of a non-ionic surfactant (Carballo-Pedrares, Kattar, Concheiro, Alvarez-Lorenzo, & Rey-Rico, 2021). The androgenic steroid system(cholesterol) is a critical component of the cell surface that helps with bilayer stiffness and has a great impact on the permeability and fluidity of the bilayer (Verma *et al*., 2021). Chitosan (CS) is one of the most used cationic polysaccharides made via N-deacetylation. Having the sustained release property, by releasing the timolol for longer, timolol-loaded chitosan-based niosomes have demonstrated a sustained impact in lowering the intraocular pressure (IOP)(Kaur, Aggarwal, Singh, & Kakkar, 2010). Timolol maleate niosomes were more effective for 8 hours in a glaucoma

rabbits when they were coated with chitosan and the intraocular pressure was reduced for a longer period of time than its typical dosage form which lasts for 2 hours. Niosomes mainly are composed of cholesterol, charged molecules, and surfactant. (Abdelkader, Wu, Al-Kassas, & Alany, 2012; Khatol, Saraf, & Jain, 2018; R. K. Sahoo *et al*., 2014).

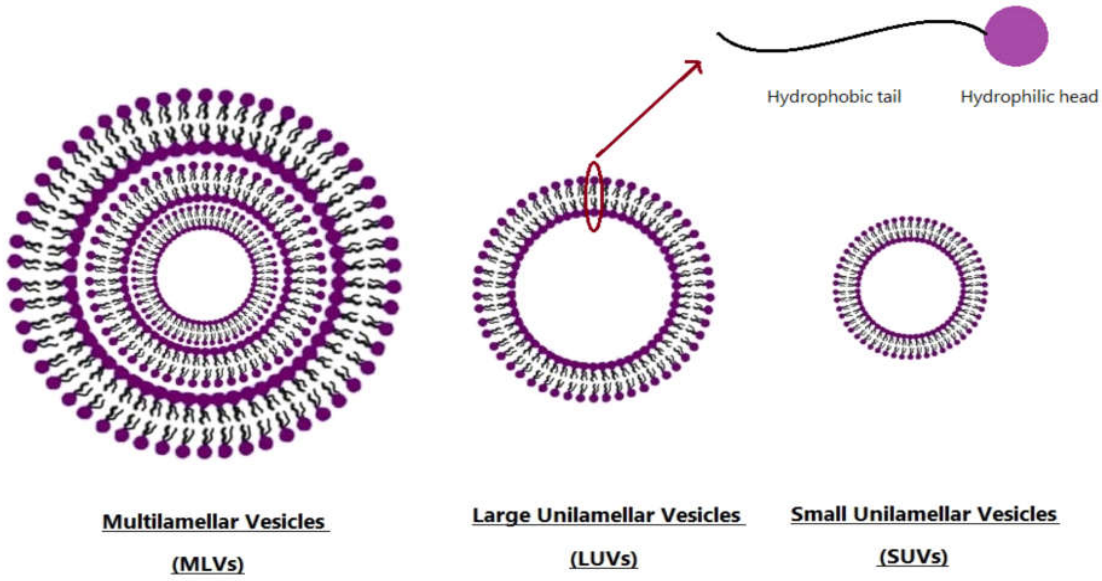

Fig-2: Typical sizes of niosomes (MLVs) Multilamellar Vesicles, (LUVs) Large Unilamellar Vesicles, (SUVs) Small Unilamellar Vesicles (Durak *et al.*, 2020).

Timolol maleate encapsulated in a noisome has approximately 2.5 times higher ocular bioavailability than timolol maleate solution. Due to easy passage through the ocular barrier and lower drug frequency and toxicity, niosomes can localize and maintain drug activity at its site of action when given an ophthalmic gel. As a result, the pre-corneal residence time is prolonged, which significantly improves ocular bioavailability (Jain, Verma, & Jain, 2020).

Table 1. Niosomal Formulations of Timolol maleate

Nano formulation	Methodology	Drug	Key component	Reference
Niosomes	Thin film hydration	Timolol maleate	Sustainable release with entrapment efficiency of 98.8%	(Ramadan, Eladawy, El-Enin, & Hussein, 2019)
Niosomes	Shake flask method	Timolol maleate	Prolonged release with entrapment efficiency of 97.700.80%,	(Lokapur, Goudanavar, Lokapur, Acharya, & Murtale, 2022)

2.2. Liposomes

Due to the amphiphilic nature of the phospholipid bilayer and an aqueous core, liposomes are able to carry hydrophilic and hydrophobic drugs with equal efficacy. Being lipid in nature due to the outer layer, liposomes tend to be highly biocompatible and biodegradable. All these features make liposomes an effective and favorable drug carrier for ocular delivery. (Lopez-Cano, González-Cela-Casamayor, Andres-Guerrero, Herrero-Vanrell, & Molina- Martinez, 2021)

A study carried out in 2022 showcased the slow release of timolol/brimonidine from cationic liposomes. Prepared by thin layer hydration technique, cationic liposomes containing a combination of 0.5% timolol and 0.2% brimonidine, with a size of 214.5 ± 19.43nm were studied for penetrability and reduction in intraocular pressure (IOP). With an entrapment efficiency of 41.36 % for timolol and 22.36% for brimonidine, these liposomes released the drugs over a period of 12 hours, providing a sustained release effect. This was further confirmed by the prolonged reduction of IOP in rabbit eyes with Hydroxypropylmethylcellulose (HPMC) induced glaucoma. In comparison to the control and aqueous solution, Timolol/brimonidine liposomes significantly reduced IOP from 21.65 ± 0.7 mmHg to 18.77±0.55 mm Hg in the first 2 hours of induction and prevented further increase (Bigdeli, Makhmalzadeh, Feghhi, & Soleimani Biatiani, 2023). Similarly, co-loaded nanoliposome containing timolol maleate and acetazolamide was prepared by thin hydration and method and compared against the control preparation of liposomes containing single drugs. The co-loaded formulation showed a reduction of 37.29± 2.86% which was greater than the reduction by individual drug liposomes. Moreover, the duration of action was also prolonged with the release of drugs being fast and sustained (Arroyo-García *et al*., 2021).

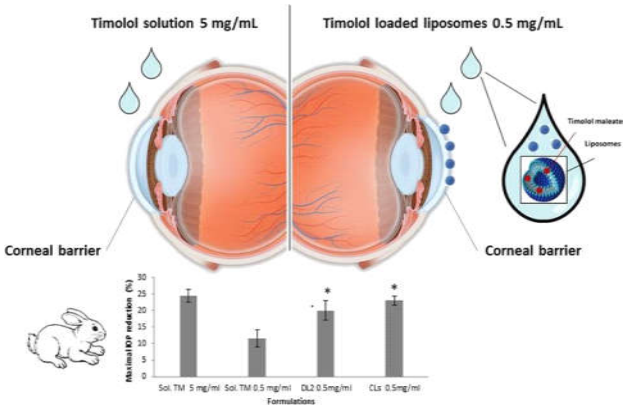

Fig-3: Maximal IOP (intraocular pressure) Reduction (%)comparison of Formulations Timolol solution 5 mg/ml vs. Timolol loaded liposomes 0.5 mg/ml (Arroyo *et al*., 2018).

In a 2018 study, prepared unilamellar nanoliposomes provided the same hypotensive effect as conventional timolol solution but at a tenfold lower dose. Timolol was fully released in the first two hours of analysis and was able to cross the corneal membrane effectively (Arroyo *et al*., 2018).

Thus, nanoliposomes have proven to be a convenient drug delivery system for timolol maleate.

Table 2. Liposomal Formulations of Timolol maleate

Nano formulation	Methodology	Drug	Key component	References
Cationic Liposome	Thin Hydration Method	Timolol maleate/Brimonidine	A sustained 12 hr. release of drug.	(Bigdeli *et al.*, 2023)
Co-loaded Nanoliposome	Thin Hydration Method	Timolol maleate/Acetazolamide	Enhanced reduction of IOP.	(Arroyo-García *et al.*, 2021)
Unilamellar Nanoliposome	Thin Hydration Method	Timolol Maleate	Tenfold lower dose requirement	(Arroyo *et al.*, 2018)

2.3. Cubosomes

Cubosomes are lipid-based vesicular nano-sized bodies with cubic structures, composed of biodegradable lipids. Cubosomes are formed by a lipid cubic base along with outer corona based on the polymer used for stabilization. A continuous periodic membrane lattice structure formed by a single lipid bilayer forms the composition of bicontinuous lipid cubic phases (Barriga, Holme, & Stevens, 2019). Due to their increased surface area as they are like honeycomb structures, cubosomes provide high drug load and protein load as compared to liposomes. The size ranges from 100-500 nm, acting as a permeation enhancer for corneal and other dermal layers, thus providing application in ocular, dermal and cancer therapy. Any drug molecule that is hydrophilic, lipophilic, or amphiphilic can be incorporated in cubosomes providing a promising approach for enhancing biocompatibility.

Two main approaches carried out for the formation of cubosomes are the top-down approach and the bottom-up approach(Rizwan & Boyd, 2015). The goal for both formulation methods remains optimal drug release and safety. The generally used technique is a top-down approach yielding cubosomes that are stable against aggregation for over one year.

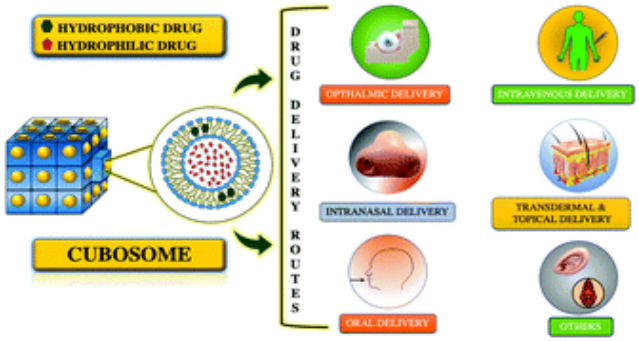

Fig-4: Routes of Cubosomal Drug Delivery (Abourehab *et al.*, 2022)

According to research carried out in 2017, cubosomal drug delivery system for Timolol maleate was constructed. Most commonly used method for the preparation of cubosomes- top-down approach is used in this study that involved the uses of glycerol monooleate and suitable stabilizer such as poloxamer 407 under high pressure homogenization for the preparation of TM cubosomes (crystalline nanoparticle in liquid form).when characterized using transmission electron microscopy the constructed liquid crystalline nanoparticle were found to have particle size of 142 nm on an average with the zeta-potential -6.27mV with encapsulation efficiency of greater than 85%. However, The solid evidence of high encapsulation efficiency and increased physicochemical stability was given by using small angle X-ray scattering (SAXS) and polarized light microscopy, also the TM cubosomes have cubic liquid crystalline D-type (Pn3) structure. Experimentation done ex-vivo suggested that corneal permeability for TM cubosomes penetration was significantly higher ocular drops available in markets. Whereas in-vivo studies in rabbits showed effective results in decrease in IOP from 27.8-39.7 to 21.4-32.6mmHg after 1 week of administration. It was also revealed that retention time for TM cubosomes was increased along with null cytotoxic effects or any irritation or ocular degeneration. Thus, making cubosomes a promising approach for remediation of ocular diseases by increasing bio-availability of TM (Huang *et al*., 2017).

Mucoadhesive Timolol maleate liquid crystalline cubogel proved to increase the dosing interval with effectively enhanced retention time hence, remediating glaucoma (Acharya, Goudanavar, & VinayC, 2019). Cubosomalnano formulation drug delivery systemhas also been used for other anti-glaucomatic drugs such as brimonidine (Emad Eldeeb, Salah, & Ghorab, 2019), cardiology laciplex (Hassan, Abdelmonem, & Abdellatif, 2018), and acetazolamide (Teba, Khalil, & El Sorogy, 2021).

Table 3. Cubosomal formulations of Timolol maleate

Nano formulation	Methodology	Drug	Key component	References
Cubosomes (liquid crystalline)	Top-down approach	Timolol maleate	Cubosomes timolol maleate with over 85% encapsulation efficiency.	(Huang *et al*., 2017)
Cubogel (mucoadhesive liquid crystalline)	Top-down approach(cubosomes) Cubogel (in-situ formulation)	Timolol maleate	Increased drug residence time in ocular tissues due to mucoadhesive nature	(Acharya *et al*., 2019)

2.4. Nanofibers:

Another massive research area in the nanometric range is nanofibers. Nanofibers are gaining researchers' attention as drug carriers for local drug delivery. Not only can these nanofibers be used as such for delivery but can also be combined with other nanotechnologies, such as nanoparticles, for enhanced delivery. Nanofibers can be prepared by mechanical and electrical forces, the latter of the two is currently the most used method. Electrospinning is an exceptional technique that depends upon electrostatic forces to produce nanofibers of variable sizes and morphology. The produced nanofibers have nano sizes but a large surface-to-volume ratio that provides a chance of greater interaction. Furthermore, the drug loading capacity is high and so is the permeation, resulting in improved therapeutic efficacy and retention at the site of action. In 2022 study, different nanofiber formulations using polycaprolactone (PCL) alone and in combination with cellulose acetate (CA) and eudragit were prepared using an electro-spinning technique. Timolol maleate was loaded at 10% w/w of polymers and release profiles, mucoadhesive properties, and in-vivo studies were carried out. In vitro release 2 step release first major burst in 12 hr. then prolonged release for up to 3 days. PCL mixed with cellulose and eudragit showed better mucoadhesion with an adhesion time of 133 and 128 seconds. Glaucomatous equine eyes were employed for in vivo studies and PCL-CA was used for evaluation. A residency time of up to 6 days with no irritancy was observed and there was a 5mmHg reduction in intraocular pressure (IOP). Thus, proving that these timolol nanofibers provide a prolonged release and can be employed for improving patient compliance (Mirzaeei *et al*., 2022).

Self-assembling hydrogels containing nanofibers are also under study for the controlled release of timolol maleate and its combinations. These self-assembling peptide hydrogels provided a 24 hr. IOP reduction with increased corneal permeability. Resultantly, there is better absorption of the drug producing in a four-fold increase in maximum plasma drug concentration (Cmax) and bioavailability (Karavasili *et al*., 2017; Taka *et al*., 2020).

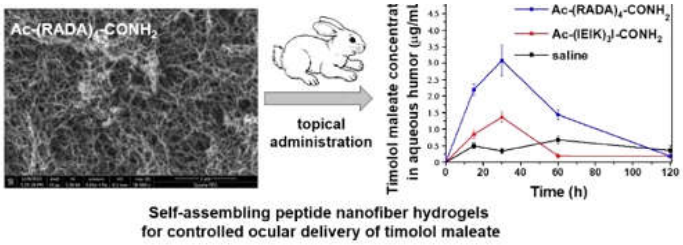

Fig-5 Self-assembling peptide nano fiber hydro gels for controlled ocular delivery of timolol maleate (Taka *et al*., 2020).

In a similar manner, the development of ocular films and contact lenses with self-assembling nanofibers and nanofibrous coating respectively is underway. These formulations reduce the need for multiple dosing while ensuring no ocular irritation, thus promising an increased residence time and sustained drug delivery (Andreadis *et al*., 2022; Mehta *et al*., 2017).

Table 4. Nanofibrous formulations of timolol maleate

Nano formulation	Methodology	Drug	Key component	References
Nanofibers	Electrospinning	Timolol maleate	Prolonged release with better mucoadhesion	(Mirzaeei *et al.*, 2022)
Nanofibers in self-assembling hydrogels	Electrospinning	Timolol maleate	Enhanced corneal permeability with Four-fold increase in Cmax	(Taka et al., 2020)
In-situ nanofibrous ocular films	Electrospinning	Timolol maleate	Faster onset of action and sustained delivery	(Andreadis *et al.*, 2022)
Nanofibrous contact lens coating	Electrospinning	Timolol maleate	Burst release with 24 hr. sustained drug release	(Mehta *et al.*, 2017)

2.5. Nanoparticles

Ocular medication delivery has utilized a variety of nanoparticle types, including dendrimers (Holden *et al*., 2012), solid lipid nanoparticles (SLN) (Attama, Reichl, & Müller-Goymann, 2009), lipid-based nanocarriers (LNC) (Puglia *et al*., 2015), and biotic (natural or synthetic) nanoparticles(S. K. Sahoo, Dilnawaz, & Krishnakumar, 2008). They are composed of macromolecular substances in which the drug is adsorbed or bonded, or the drug is dissolved, trapped, or encapsulated within (Rençber, Bülbül, Senyigit, Okur, & Siafaka, 2023). Nanospheres and nano-capsules are two categories into which nanoparticles can be sorted. Drugs may either be integrated into the nanospheres' matrix or adsorbed onto the colloidal carrier's surface. Whereas, a core cavity and a polymeric membrane surround a small capsule known as a nano-capsule (Rollot, Couvreur, Roblot-Treupel, & Puisieux, 1986).

Due to their ability to protect encapsulated molecules, facilitate transport to the various ocular compartments, and provide the prolong release of medication, nanoparticles (NPs) have received a lot of interest lately (Shukla, Mishra, Arotiba, & Mamba, 2013).

2.5.1. Gelatin based nanoparticles (GNPs)

Gelatin is an excellent choice for ocular administration due to a number of its advantages. Collagen, the natural precursor of gelatin, for instance, can be found in the stroma, or inner layer, of the cornea (Friess, 1998). Additionally, the muco-adhesive qualities of gelatin increase its retention period by interacting with the negatively charged mucus layer through the positively charged amine groups, making gelatin the best natural carrier for ocular medication delivery (Hathout & Omran, 2016).

Different preparation methods have been employed by different researchers. For instance, single-desolvation, double-desolvation, concertation, emulsification/micro emulsification, and more recently, nanoprecipitation (Yu, Chu,

Cai, Tong, & Yao, 2014). As a result, in 2018 a research was conducted to prepare gelatin nanoparticles, which were created utilizing a two-step desolvation process and then they were enhanced using a full-factorial design before being characterized(Shokry, Hathout, & Mansour, 2018). The effectiveness of the newly created medicinal product was assessed by measuring the intraocular pressure and comparing it to the commercialized timolol maleate 0.5% eye drops.

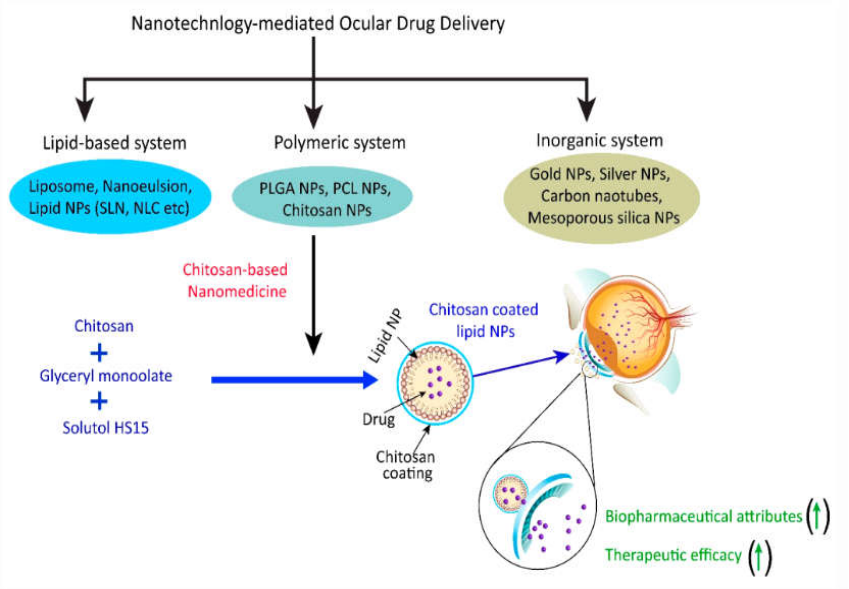

Fig-6: Nanotechnology-mediated Ocular Drug Delivery, (NPs) Nanoparticles, (SLN) Solid Lipid Nanoparticles, (NLC) Nanostructured Lipid Carriers, (PLGA) Poly lactic-o-glycolic Acid, (PCL NPs) Polycaprolactone Nanoparticles (Albarqi *et al*., 2023)

In the study different concentration models for Timolol maleate GNPs were prepared, and it demonstrated that Timolol maleate GNPs with the highest glutaraldehyde (GA) concentration (1:2) and longest crosslinking period (16 h) have the best results for average diameter (205nm) and polydispersity index (0.014) but these nanoparticles have a low zeta potential (12.5 mV) (Shokry *et al*., 2018) and have a stable, homogeneous shape (Elzoghby, Samy, & Elgindy, 2012). Over a six-month period, the stability of the prepared formulation was monitored, and the drug's entrapment efficiency was 73.41 0.63%, exceeding 98% of the initial loaded quantity. The TM GNP formulations showed higher effectiveness compared to market eye drops (Shokry *et al.* 2018) due to gelatin's muco-adhesive properties that made it easier for substances to interact with intraocular compartments thus, the pre-corneal residence period with GNP formulation appears to have increased (J. Singh, Chhabra, & Pathak, 2014).

The TM GNPs formulation maintained a sustained impact, with an average 24 hr. IOP decrease of 52% after initial therapy, compared to the market eye drops' 31% reduction. Thus, gelatin nanoparticles effectively deliver timolol maleate, achieving high efficiency, stability, and bioavailability, making them a promising new glaucoma treatment (Shokry *et al*., 2018).

2.5.2. Chitosan based polymeric nanoparticle

The majority of polymeric nano-formulations are built on natural polymers, which have proven to be suitable carriers for delivering medication topically through the constrained pre-corneal area and releasing them over a long period of time. Chitosan (CS) was frequently employed as a transcorneal absorption enhancer in the administration of ocular drugs due to its high mucoadhesion. For ocular applications, CS nanoparticles (NPs) can encapsulate a variety of medications while preserving their biological action as anti-bacterial or anti-inflammatory medicines. NPs of CS are also able to interact and stay linked with the ocular mucosa for prolonged periods of time. Additionally, because of its hydrophilic qualities, chitosan is a good medication carrier for hydrophilic substances (Siafaka *et al*., 2015).

In research, conducted in 2017, Galactosylated chitosan (GC) nanoparticles (TM-GC-NPs) were created with timolol maleate (TM) as the loading agent. The ion cross-linking method was used to make TM-GC-NPs. The optimized nanoparticles had a particle size of 213.3 ± 6.83 nm a 38.58 ± 1.31% entrapment efficiency, and a 17.72 ± 0.28%. drug loading. According to the in vivo pharmacodynamics investigation, the formulation greatly increased the drug's efficacy and bioavailability. The TM-GC-NP formulations are therefore regarded as a better delivery strategy for the treatment of glaucoma on the basis of evaluation and comparison with the commercial timolol eye drops and TM-CS-NPs (Zhao *et al*., 2017).

Research from 2018 stated, the pre-gelation approach was effectively used to create CS-SA NPs loaded with TM as a targeted drug delivery carrier for the treatment of glaucoma. The results indicated that the form and size of the nanoparticles were spherical and in the range of 80-100 nm, and the release profiles for in vitro demonstrated that CS-SA NPs have sustained release and the penetration of TM was greatly increased. About 42% and 94%, respectively, of the loading capacity and encapsulation efficiency were achieved. They showed a rapid release of the drug within the first hour, followed by a more gradual release of the drug over the following 24 hours. The findings also showed that TM laden with nanoparticles penetrated the cornea twice as deeply as TM (Ilka *et al*., 2018).

2.5.3. Gold nanoparticles (GNPs)

In ophthalmology, the use of gold nanoparticles (GNPs) for diagnostic and therapeutic purposes has shown considerable progress. Their distinctive nanoscale characteristics, including their variable size and shape, surface plasmon resonance, and bioco- mpatibility, make them useful instruments in a variety of ophthalmic applications (Arvizo, Bhatta- charya, & Mukerjee, 2010).

A study conducted in 2018 stated, Trisodium citrate dihydrate was used to reduce chloroauric acid (HAuCl4) to produce gold nanoparticles (GNPs), which were spherical and ranged in size from 50 to 100 nm. These nanoparticles were used to load timolol at a concentration of 4 mg/ml through a soaking solution in the lens, improving the bioavailability of the drug. In vivo, the pharmacokinetic analysis showed consistently higher timolol concentrations in tear fluid throughout various time points compared to the conventional soaking approach, despite following a similar release pattern. In vitro, flux data indicated no significant enhancement in timolol release rates for both methods. A sustained intraocular pressure (IOP) drop when compared to standard

to standard soaking demonstrated by pharmacodynamic analysis. The iris-ciliary muscle, conjunctiva, and sclera all showed elevated timolol accumulation according to tissue distribution analyses. The increase of ciliary muscle, which contains the bulk of b-receptors, may be responsible for the prolonged IOP drop.In summary, the incorporation of GNPs into contact lenses has shown the potential to increase timolol absorption, resulting in beneficial in vivo kinetic and dynamic outcomes without jeopardizing lens integrity (Maulvi e*t al*., 2019).

2.5.4. Molecularly Imprinted Polymer Nanoparticles

Synthetic cross-linked polymers having particular molecular recognition sites are known as molecularly imprinted polymers (MIPs) (Aeinehvand, Zahedi, Kashani-Rahimi, Fallah-Darrehchi, & Shamsi, 2017). Due to the numerous functional interaction sites, that are available for complex formation during MIP production, timolol maleate (TM), which is the primary therapeutic agent for treating glaucoma, makes a great drug model for the creation of MIP-based controlled release systems. In 2016 a study was conducted that evaluated monomer compositions, including 2-hydroxyethyl methacrylate (HEMA), to design non-toxic, selective, and biocompatible MIP NPs for sustained control release of TM via precipitation polymerization, potentially for ocular disease therapeutic delivery. The study showed that synthesized nano-sized MIP particles with an average diameter of 128 nm using a 10:1 HEMA:TM ratio and acetonitrile as the porogenic solvent. These MIP NPs showed high drug molecule selectivity and chemisorption on molecularly imprinted poly (HEMA) surfaces for adsorbing TM. Biocompatibility tests confirmed their non-toxic nature and the in vitro drug release showed a slower profile in phosphate-buffered saline. Thus these exceptional characteristics of MIP NPs make them suitable for ocular drug delivery applications (Aeinehvand *et al*., 2017).

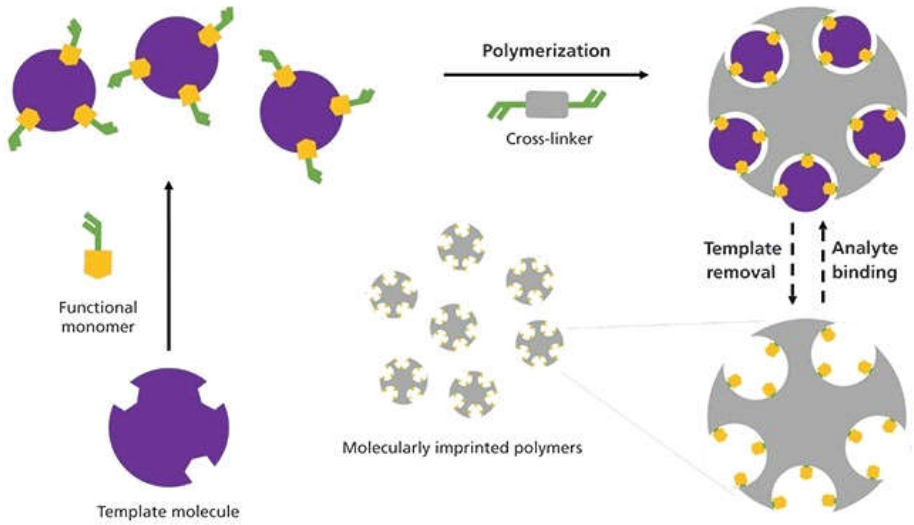

Fig-7: Preparation of Molecularly Imprinted Polymer (Bitas & Samanidou, 2018)

Table 5. Formulations containing nanoparticles of Timolol maleate

Nano formulation	Methodology	Drug	Key component	Reference
Gelation based Nanoparticles	Two step desolvation process	Timolol maleate	Drug's entrapment efficiency is 73.41 0.63%,	(Shokry *et al*., 2018)
Galactosylated chitosan (GC) nanoparticles	Ion cross-linking method	Timolol maleate	Optimized nanoparticles with entrapment efficiency of 38.58 ± 1.31%	(Zhao *et al.*, 2017)
Chitosan (GC) nanoparticles	Pre-gelation approach	Timolol maleate	Penetration of the cornea twice deeply	(Ilka *et al.*, 2018)
Poly (sulfobetaine methacrylate) based nanoparticles	Reversible addition-fragmentation chain transfer polymerization	Timolol maleate	Steady release up to the tenth hour with a loading efficiency of 23%	(Nikolova, Ruseva, Tzachev, Christov, & Vassileva, 2022)
Poly(2-hydroxyethyl methacrylate)-based molecularly imprinted polymer nanoparticles	Precipitation polymerization	Timolol Maleate	nano-sized MIP particles of diameter=128 nm	(Aeinehvand *et al*., 2017)

3. CONCLUSION

Glaucoma is a catastrophic condition affecting people worldwide. Although effective anti-glaucoma medications have been created over time, issues including poor patient compliance, undesirable side effects, narrowed bioavailability and ineffective delivery systems restrict their clinical efficacy. This review article focuses on the intriguing method that makes use of timolol maleate in nano-formulations, which can precisely target the afflicted regions to offer prolonged drug release, halting the progression of glaucoma.

It is also vital to stress that ongoing research efforts should concentrate on developing novel therapies and that before scaling up and securing market clearance for such preparations, inclusive safety evaluations must be carried out.

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