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# Nanomedicine in glaucoma treatment; Current challenges and future perspectives

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ABSTRACT

Glaucoma presents a significant global health concern and affects millions of individuals worldwide and predicted a high increase in prevalence of about 111 million by 2040. The current standard treatment involves hypotensive eye drops; however, challenges such as patient adherence and limited drug bioavailability hinder the treatment effectiveness. Nanopharmaceuticals or nanomedicines offer promising solutions to overcome these obstacles. In this manuscript, we summarized the current limitations of conventional antiglaucoma treatment, role of nanomedicine in glaucoma treatment, rational design, factors effecting the performance of nanomedicine and different types of nanocarriers in designing of nanomedicine along with their applications in glaucoma treatment from recent literature. Current clinical challenges that hinder real-time application of antiglaucoma nanomedicine are highlighted. Lastly, future directions are identified for improving the therapeutic potential and translation of antiglaucoma nanomedicine into clinic.

## 1. Introduction

Glaucoma a silent killer of eye sight comprises a diverse group of conditions resulting into irreversible vision loss characterized by gradual loss of retinal ganglion cells (RGCs), damage to optic nerve and often associated increased pressure inside the eye [1,2]. Due to gradual decline in eye sight, the continual asymmetry of disease condition between eyes and the neurological mechanism responsible for area of omitted vision, many patients are usually unaware of their visual impairment until the latter stages of the disease [3,4]. According to the published report of World Health Organization (WHO) "world report on vision" claims in 2020 that 76 million peoples are suffering with glaucoma and predicted a substantial increase of 1.4 times (111 million) by 2040 [5]. In China, the yearly costs for early treatment of glaucoma is approximately $945, rising to $12520 annually for bilateral eye sight loss. This cost might be compared with per-capita gross domestic product (GDP) of China's urban ($10,800) and rural regions ($4010) [6]. Though glaucoma is the prime cause of permanent blindness around the world, however most of the glaucoma patient retain their functional eye sight throughout the life spin and the treatment is only effective in decelerating the loss of eye sight from glaucoma. Globally, approximately 95 million individuals are affected by glaucoma, with over 10 million experiencing blindness in at least one eye [7]. Additionally, a significant number of individuals have visual impairments and influencing their routine activities as a result of glaucoma.

Glaucoma can be classified into secondary and primary glaucoma. Secondary glaucoma may arise as a result of surgical interventions, drugs, or underlying medical disorders [8]. For instance, the use of topical steroids might lead to the development of secondary glaucoma and its related symptoms. Primary glaucoma further categorized into:

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primary open-angle glaucoma (POAG) and closure-angle glaucoma [9]. POAG is the predominant form of glaucoma, representing 75 % of all glaucoma cases worldwide [10,11]. The angle-closure glaucoma and POAG have different pathologies that causes increase in ocular pressure. In POAG, the increased ocular pressure is instigated by reduced outflow of aqueous humor due to blockage in trabecular meshwork (Fig. 1). This increase in ocular pressure occurs progressively over the time and usually without the patient's awareness until there is a severe loss of vision. On the other hand, angle-closure glaucoma occurred rapidly, when the lens exerts pressure on the iris, abruptly closing the drainage angle between the cornea and iris. This leads to a physical blockage of the outflow of aqueous humor and causes ocular hypertension [11]. However, in case intraocular pressure (IOP) remains within the normal range but still vision loss occurs due RGCs loss but the underlying cause of RGC loss is still unclear. This type of glaucoma is called primary normotensive glaucoma [9].

Although ocular hypertension is the main risk factor for POAG, other risk factors including vascular dysregulation, which is not reliant on IOP, are believed to have a greater impact on the progression of primary normotensive glaucoma. Glaucoma is highly inheritable disease and a true family history increases the risk of glaucoma in first-degree of relatives about 8-folds compare to general population [12,13].

Glaucoma is principally caused by the optic nerve damage through an apoptosis of RGCs. The apoptosis of RGCs were facilitated by two types of mechanisms. First, mechanical injury, caused by increased IOP leading to damage of RGCs (Fig. 2 A). High IOP causes stasis of axonal flow of RGCs at lamina cribrosa of optic disc, causes neurotrophic proteins (NFPs) blockage, which finally leads to RGCs apoptosis [14]. The second mechanism involve the development of local vascular insufficiency or ischemia at optic nerve head which leads to decrease in neurotrophic factors (NFs) levels, which causes death of RGCs (Fig. 2 B) [15]. In addition, dysfunction of mitochondria, excitotoxicity, oxidative stress and low cerebrospinal fluid pressure-triggered translaminar cribrosa pressure gradient might be involved in optic nerve damage during glaucoma [16,17].

## 2. Conventional glaucoma treatment and its limitations

The current objectives of glaucoma treatment are to prevent damage to the optic nerve, preserve the patient's visual field, and maintain their quality of life by minimizing the side effects of medication [18,19]. Of the several factors that might increase the risk of glaucoma development, IOP is considered the most crucial and only practicable risk factor of glaucoma. IOP reduction inhibits the progression of glaucoma. Therefore, it is essential to prioritize IOP as the first aspect to modify at the onset of therapy, and the primary recognized strategy for glaucoma treatment is the reduction of IOP [20,21]. The therapy consists of applying antiglaucoma eye drops directly to the affected area, followed by the administration of oral drugs, laser treatment, and surgery if necessary. The treatment of glaucoma can be categorized into medical therapy, laser therapy and surgery (Table 1).

Topical eye drops of antiglaucoma drugs effectively reduced the IOP, and several therapeutic agents with specific mechanisms are used [24]. For example, cholinergic agonists stimulate the contraction of the ciliary muscle, leading to a more spherical shape of the lenses and an increase in their focusing ability, and also contracted the cells of trabecular meshwork (TM), resulting in an enhanced outflow of the aqueous humor via the trabecular pathway. Alpha adrenergic agonists suppress the production of aqueous humor, whereas carbonic anhydrase inhibitors decrease aqueous humor secretion by lowering the activity of the enzyme in the ciliary body. Beta-adrenergic receptor antagonists reduce the formation of aqueous humor by the ciliary body, however they may also cause cardiac or respiratory adverse effects [25]. Prostaglandin analogues decrease intraocular pressure (IOP) by promoting the drainage of fluid via the uveoscleral pathway. However, these drugs may cause side effects include redness of the conjunctiva and the abnormal growth of eyelashes towards the eye (trichiasis). Hence, traditional topical eye drops used for treating antiglaucoma may have low tolerability, and the frequent need of reapplying them into the eye is often associated with poor compliance [23]. Furthermore, the delivery of drugs to specific tissues within the eye using topical medications has been a persistent difficulty because of the existence of physiological or dynamic (tear drainage, conjunctival lymph and blood flow) and anatomical or static barriers (corneal, blood-retinal and blood-aqueous barriers) in the human eye (Fig. 3) [26].

When antiglaucoma drug is topically administered as an eye drops, static or anatomical barriers reduced the absorption of drugs into the disease tissue inside the eye, while the dynamic or physiological barriers quickly drain the administered drug into the blood circulation. In the meantime, secondary factors, including blinking of eyes, nasolacrimal drainage and tear film turnover speed-up the drug elimination [27,28]. Approximately 10 μL of the applied formulation is believed to stay on

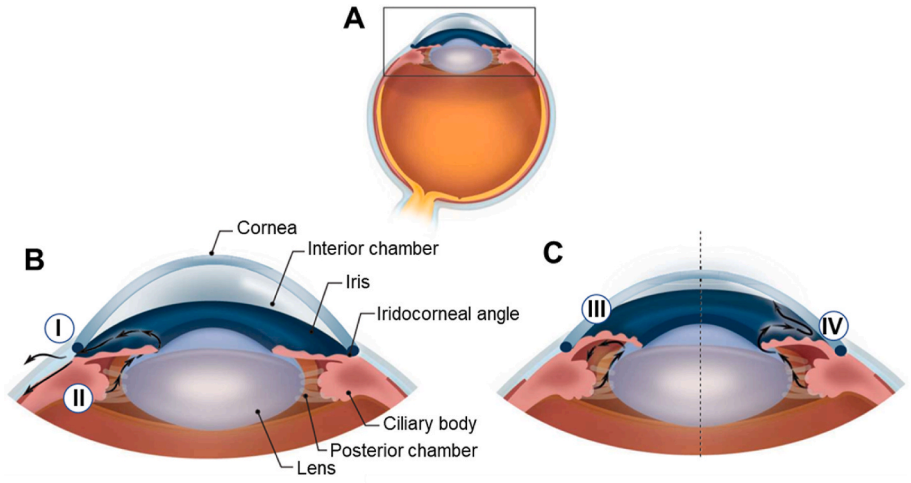


**Fig. 1.** Determination of IOP and difference between POAG and closure-angle glaucoma. (A) Location of anatomical structure in the eye that determine the IOP. (B) PAOG is characterized by an open drainage angle. (I) IOP is determined by the amount of aqueous humor produced by the ciliary body. (II) The amount of aqueous humor draining from the eye via drainage pathway located at iridocorneal angle. Black arrows represented the aqueous humor direction inside eye. (C) Closure-angle glaucoma characterized by aqueous humor unable to reach the drainage pathway located at iridocorneal angle causes elevated IOP. This might be caused by two mechanisms. (III) Angle closure, in which peripheral iris blocking access to drainage pathway. (IV) Pupil block, in which contact between pupil and iris blocking aqueous flow. Reproduced from Ref. [11] with permission from Elsevier.

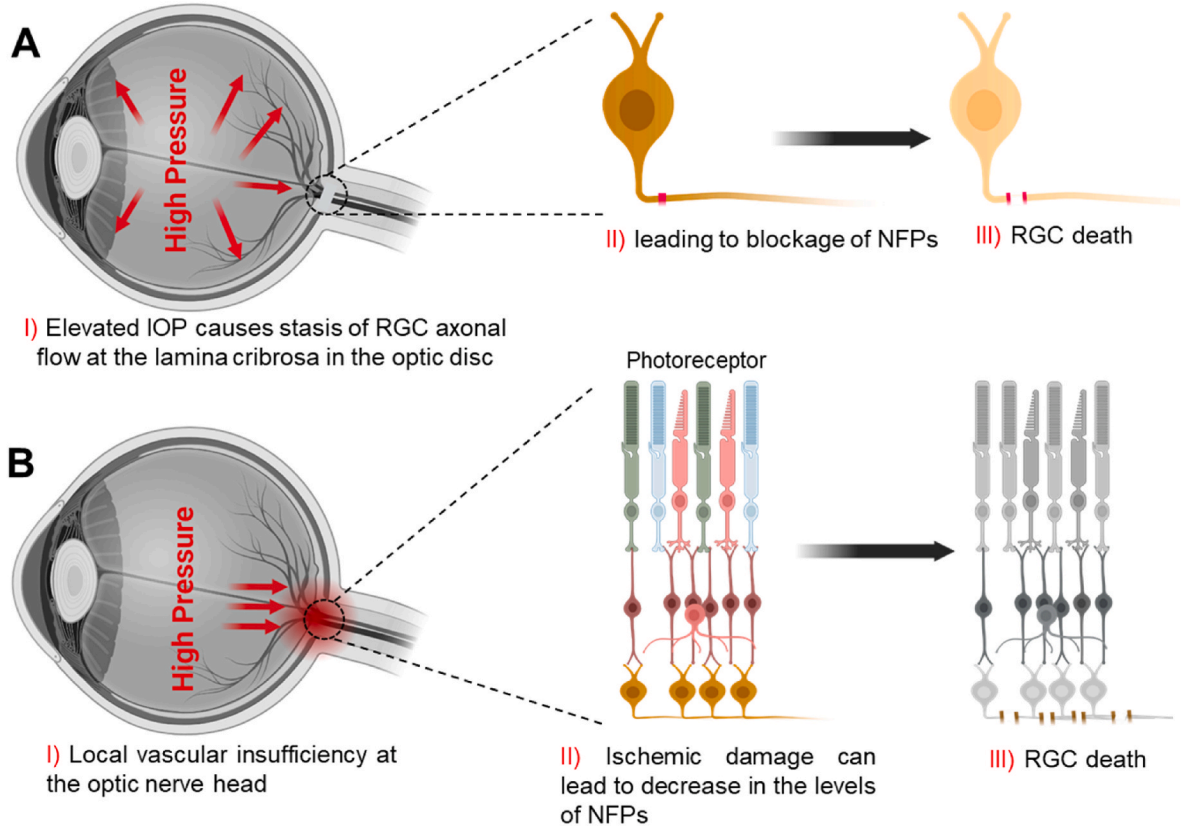


**Fig. 2.** Optic nerve damage mechanisms in glaucoma (A) The IOP elevation (B) Local vascular deficiency at optic nerve head causes the neurotropic proteins blockage leading to RGCs death.

**Table 1**
Current glaucoma treatment.

| Type of treatment | Therapeutic modalities/procedure | References |
|---|---|---|
| Medical therapy | Cholinergic agonist, prostaglandin agonist, carbonic anhydrase inhibitor, beta blocker, alpha adrenergic agonist | [22] |
| Laser therapies | Trabeculoplasty, cyclophotocoagulation, iridoplasty, iridotomy | [23] |
| Surgical therapies | Trabeculectomy, viscocanalostomy, deep sclerectomy, glaucoma drainage implants, goniotomy, trabeculotomy | [22,23] |

the surface of the eye after a single blink of eye, and almost all administered formulation is cleared from the eye's surface within 15–25 min allowing a short duration of about 5–7 min for absorption of administered drug [29]. Eventually, around 5 % of topically administered formulation may overawed the barriers and reached to the anterior segment of eye, thus recurrent administration is required, which leads to patient incompliance and early termination of medication [30–32]. These ocular barriers also play a role in the fluctuating therapeutic effect that occurs before and after each application of the eye drops [3]. The variation in medication concentrations over time might cause fluctuations in IOP at various times intervals of the day, which is likely to contribute to the development of glaucoma [33].

Sometime, medical therapy may not effectively reduce the IOP to the desired levels, despite the use of the most effective medications for management of glaucoma, the disease may still progress and lead to the degradation of the optic nerve [23]. In such cases, trabeculoplasty may be investigated as a treatment option to decrease IOP in patients with open-angle glaucoma. Argon laser trabeculoplasty (ALT) involve targeting the TM cells carrying pigment with laser, triggering coagulative necrosis as well as thermal damage which induce the contraction of the TM, hence increasing the drainage capacity of the aqueous humor [34–36]. The argon laser's harm extends beyond the target region containing melanin protein. The use of ALT might result in significant adverse effects, including peripheral anterior synechiae, uveitis, and temporary increases in IOP [37]. Conversely, a Q-switched Nd:YAG laser with double frequency is used for the purpose of selective laser trabeculoplasty (SLT). SLT decreases IOP by various mechanism, including the stimulation of cell and extracellular matrix (ECM) synthesis and turnover, displacement of trabecular cells, and mechanical enlargement of the Schlemm's canal [38]. SLT, unlike ALT, precisely targets the TM carrying pigmented cells, reducing damage to nearby cells both structurally and thermally. Laser iridotomy reduces the risk of an acute angle closure glaucoma attack. Diode laser cycloablation effectively eradicates the ciliary body, resulting in a reduction in IOP by inhibiting the production of aqueous humor [39].

The decrease in glaucoma surgeries may be attributed to the advancement of pharmacotherapy [40]. The primary objective of conventional glaucoma surgery is to create a passage in the TM that facilitates the drainage of aqueous humor, leading to a decrease in IOP. Trabeculectomy, also known as TVT, aims to remove a portion of the TM in order to enhance the drainage of aqueous humor [41]. However, TVT might be ineffective due to the excessive scarring surrounding the passage, excessive outflow leading to hypotony, and detachment of the choroid. The tube vs. TVT trial has confirmed the increased use of glaucoma drainage implants, which are now becoming more popular even in non-refractory glaucoma cases [42,43]. Glaucoma surgery is associated with a significant incidence of complications, including hypotony, shallow anterior chambers, choroidal effusions, and hyphema. In addition, potential long-term complications such as blebitis, wound leaking, and endophthalmitis might be associated with glaucoma surgeries [44].

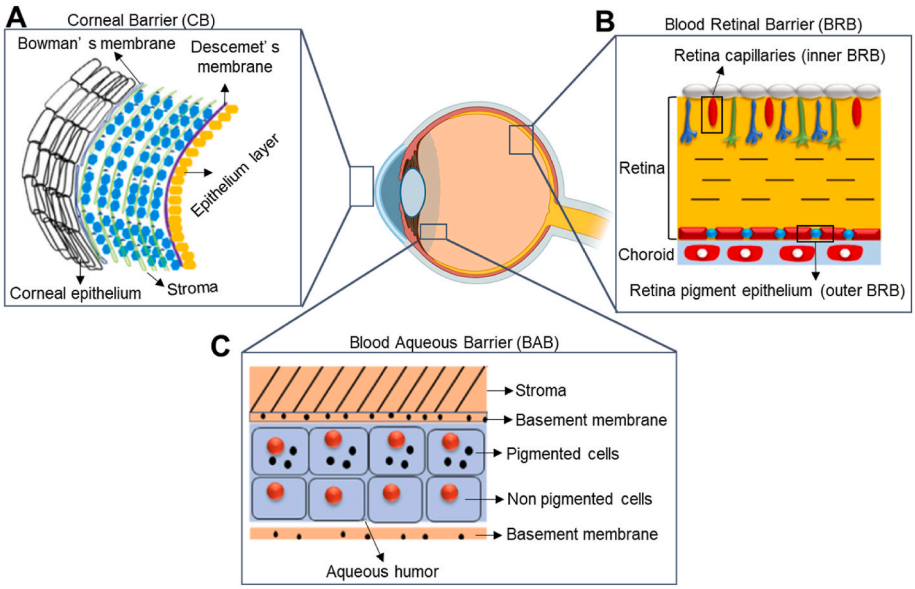


**Fig. 3.** Anatomical or static barriers to ocular drug delivery. (A) Corneal barrier: comprises of epithelial layers connected together via tight junctions followed by endothelial cells and dense stroma avoiding the entry of antiglaucoma drugs. (B) Blood retinal barrier: composed of the inner and outer BRB involved retinal capillaries and retinal pigmented epithelium. (C) Blood aqueous barrier: involved pigmented and non-pigmented cells of epithelial layer of ciliary body, and the endothelial layer of iris blood vessels.

Hence, it is significant to overcome the drawbacks of traditional glaucoma treatment approaches. The use of IOP-lowering drugs directly to the affected area is categorically the most important aspect of anti-glaucoma therapy. This need might be met via the recruitment of nanomedicine in glaucoma treatment [45].

## 3. Nanomedicine in glaucoma treatment

The idea of nanocarriers was first introduced in 1980s; however, the word “nanomedicine” was first officially defined by European Science Foundation (ESF) in 2003. Finally, in 2010, the precise definition of nanomedicine was established as "the extensive monitoring, regulate, construction, repair, defense, and enhancement of biological systems of human at molecular level with help of engineered nanostructures and nanodevices operating single-cell level with the ultimate goal of achieving enhanced therapeutic benefits [46,47]. Nanomedicines, a branch of nanotechnology, play a significant role in the diagnosis and treatment of various diseases, including ocular diseases, by greatly enhancing the efficacy of therapies [28,48,49].

Nanomedicines has the capacity to encapsulate a wide range of therapeutic agents. The encapsulation of drug molecule in nanomedicine protect them from degradation and also enhance the targeting ability via surface modification [50–52]. Significant efforts have been devoted in the field of ophthalmology to improve the ability of topically applied medicine to be retained and penetrate effectively to anterior segment of eye. Chitosan (CH), hydroxypropyl methylcellulose (HPMC), gellan, gelatin, hyaluronic acid (HA), and carboxymethylcellulose are often used as a mucoadhesive agents in the formulation of nanomedicines to extend the retention time on ocular surface and may show resistance to ocular clearance as a result of the movement of blinking and the impulsive production of tears [53–55]. Furthermore, the outermost layer of the cornea, known as the superficial corneal epithelium, is coated with a mucin membrane that carries a negative charge. This creates an ideal surface for attaching nanocarriers that have a positive charge [56,57].

For instance, the cationic polymer CH has strong adhesive capabilities to mucous membranes. This is because it creates electrostatic interactions when it comes into close contact with the surface of the eye. Additionally, CH has the ability to open the tight junctions between cells, making it an effective enhancer for the penetration of substances. This makes CH a suitable candidate for improving the delivery of drugs or other compounds to the eye [58,59]. CH has attracted the researcher’s attention because it can be easily modified and has fully fortified characteristics; such as an enhanced antidegradation abilities achieved by increasing the deacetylation degree of the CH component, as well as antioxidant activities resulting from methoxylation effects or kaempferol conjugation [60,61]. One important factor to be considered for chronic disorders like glaucoma treatment is the controlled and continuous drug release of pharmaceuticals. This may be achieved by carefully designing the parameters of nanomedicines.

The encapsulation of therapeutic agents into nanomedicine may surpass the drawbacks of current treatment strategies by enhancing the drug penetration, attaining target-specific delivery, extending the contact of cargo drugs with ocular surface, and *in vivo* sustained drug release [62–64]. In addition, nanomedicines are also effective in transporting the hydrophobic drug molecules, proteins and genes (DNA or RNA), which are difficult to be deliver with conventional solvents [65]. Nanomedicines also have the capacity to protect the cargo drug integrity before delivering to the desire sites. This property of nanomedicine is particularly captivating when delivering highly sensitive protein molecules like antibodies and neurotrophin which can easily degrade *in vivo* [66]. Recent five years (2019–2024) case studies of nano drug delivery systems loaded with IOP lowering drugs for glaucoma treatment has been summarized in Table 2.

In glaucoma treatment, nanomedicine offers promising strategies to inhibit the formation of aqueous humor or promote its outflow, thereby helping to manage intraocular pressure and prevent further optic nerve damage. Nanomedicine can be engineered to release antiglaucoma drugs that act on targets such as adrenergic receptors or carbonic anhydrase enzymes in the ciliary body, which are involved in the secretion of aqueous humor as a result production of aqueous humor reduced and subsequently lower IOP. Nanomedicine designed for anti-glaucoma therapy can also facilitate the outflow of aqueous humor and lowering the IOP either by enhancing the function of the trabecular meshwork or targeting the Schlemm’s canal. So, nanomedicine with drug molecule that promote the relaxation of the trabecular meshwork or disrupt extracellular matrix or enhance the contractility or permeability of the Schlemm’s canal endothelial cells, could improve the

**Table 2**
Case studies of nanomedicine for glaucoma treatment.

| Drug | Nanocarrier | Dosage | Application/Advantages | Year | Ref. | Status |
|---|---|---|---|---|---|---|
| Timolol | Gold NPs (GNP) | Contact lenses | Bioavailability enhancement | 2019 | [67] | Pre-clinical |
| Dorzolamide | Galactomannan NPs | Drops | Increased corneal penetration ability, prolonged drug action time with sustained drug release | 2019 | [68] | Pre-clinical |
| Brimonidine | Chitosan NPs | Drops | Prolonged drug action time with sustained drug release | 2019 | [69] | Clinical |
| Pilocarpine | Ce-CS NPs | Drops | Enhance corneal penetration ability, Targeted drug release | 2020 | [70] | Pre-clinical |
| Pilocarpine | Polylactic acid (PLA) NPs | Drops | Prolonged drug action time with sustained drug release | 2020 | [71] | Pre-clinical |
| Travoprost | DNA NPs | Drops | Increased corneal penetration ability | 2020 | [72] | Pre-clinical |
| Travoprost | Nanoemulsion | Drops | Prolonged drug action time with sustained drug release | 2020 | [73] | Pre-clinical |
| Brinzolamide | Nanoemulsion | Gel | Enhanced mucoadhesion with enhance bioavailability and sustained drug release | 2020 | [74] | Pre-clinical |
| Brinzolamide | Chitosan-pectin NPs | Drops | Increased corneal penetration ability, prolonged drug action time with sustained drug release | 2020 | [75] | Pre-clinical |
| Fasudil | PLGA NPs | Injection | Prolonged drug action time with sustained drug release and increased bioavailability | 2020 | [76] | Pre-clinical |
| Timolol | Magnesium hydroxide NPs (nMH) | Drops | Enhanced corneal permeation ability | 2021 | [77] | Pre-clinical |
| Timolol | Nanogel | Gel | Prolonged drug action time with sustained drug release | 2021 | [78] | Pre-clinical |
| Brimonidine | Lipid-DNA NPs | Drops | Prolonged drug action time with sustained drug release | 2021 | [72] | Pre-clinical |
| Brimonidine | Liposomes | Drops | Enhanced corneal permeation ability | 2021 | [79] | Pre-clinical |
| Latanoprost | Liposomes | Drops | Prolonged drug action time with sustained drug release | 2021 | [80] | Pre-clinical |
| Latanoprost | Hyaluronic acid-chitosan NPs | Drops | Reduce the application of preservatives and prolonged drug action time with sustained drug release | 2021 | [81] | Pre-clinical |
| Brinzolamide/ latanoprost | Nano-lipoidal | Drops | Increased corneal penetration ability, prolonged drug action time with sustained drug release | 2022 | [82] | Clinical |
| Dorzolamide | Chitosan/PCL NPs | Drops | Increased corneal penetration ability, prolonged drug action time with sustained drug release | 2022 | [83] | Pre-clinical |
| Dorzolamide | Nanoemulsion | Drops | Prolonged drug action time with sustained drug release and increased bioavailability | 2022 | [84] | Pre-clinical |
| Brinzolamide | Noisome | Gels | Prolonged drug action time with sustained drug release | 2022 | [85] | Pre-clinical |
| Brinzolamide | Nanofibers | Film | Enhanced mucoadhesion with enhance bioavailability and sustained drug release | 2022 | [86] | Pre-clinical |
| Travoprost | Mannitol NPs | Ocular insert/ Gel | Prolonged drug action time with sustained drug release | 2022 | [87] | Pre-clinical |
| Latanoprost | Liposomes | Contact lenses | Prolonged drug action time with sustained drug release | 2022 | [88] | Pre-clinical |
| Latanoprost | PLGA NPs | Iontophoretic | Prolonged drug action time with sustained drug release | 2022 | [89] | Pre-clinical |
| Latanoprost | Nanoemulsion | Drops | Reduce the application of preservatives and reduced cytotoxicity | 2022 | [90] | Pre-clinical |
| Brimonidine | Silica NPs | Contact lenses | Avoiding sudden drug release | 2022 | [91] | Pre-clinical |
| Brimonidine | Resins NPs | Drops | Reduce adverse reactions animal | 2022 | [92] | Pre-clinical |
| Timolol | Nanofibers | Flim | Extend the drug action time by sustained-release profile | 2022 | [93] | Pre-clinical |
| Timolol | Nanoemulsion | Gel | Extend the drug action time by sustained-release profile | 2022 | [94] | Pre-clinical |
| Disulfram/Cu(II) | Nanoparticles | Injection | Deplete reactive oxygen species and inhibit proptosis | 2022 | [95] | Pre-clinical |
| Necrostatin-1 | Nanoparticles | Injection | Targeting Cell Membranes, Depleting ROS | 2022 | [96] | Pre-clinical |
| Pilocarpine | Chitosan-cerium dioxide (Ce-CS) NPs | Drops | Controlled drug release with enhanced corneal permeation ability | 2023 | [97] | Pre-clinical |
| Timolol/brimonidine | Liposomal | Drops | Enhance corneal penetration ability, prolonged drug action time with sustained drug release | 2023 | [98] | Pre-clinical |
| Acetazolamide | Elastin like recombinamers | Drops | Enhance corneal penetration ability, prolonged drug action time with sustained drug release | 2024 | [99] | Pre-clinical |

aqueous humor drainage from eye. In addition, nanoparticles can also deliver anti-inflammatory agents or vasodilators to reduce inflammation and improve the ocular blood flow in the drainage structures, thereby facilitating the outflow of aqueous humor [100–102].

## 4. Consideration in designing of nanomedicine

The delivery of therapeutic agents to a specific cell or targeted tissue is important for several reasons. First, it facilitates therapeutic effect for longer duration at the desired site; second, endorse uniform distribution

of therapeutic agents at the desired site; third, reduced the non-specific binding of therapeutic agents to the surrounding healthy tissues, and finally, reducing the dose and dosing frequency necessary for therapeutic responses [103,104]. Particularly, in the field of ocular medicine, 90 % of current medicine are in the form of a solution, such as eye drops [105]. However, the primary obstacles in delivering medication to the eye are the quick and efficient removal caused by the turnover of tears and the drainage system of the nasolacrimal duct [106]. Furthermore, ocular formulations nature also shown additional challenges that aggravate patient compliance issues and therefore impact treatment outcomes. For example, an ophthalmic prednisolone suspension (Pred Forte$^{Tm}$) as an eye drops have been investigated for the treatment of anterior uveitis. These eye drops need to be used every 3 h for a period of 14 days in order to obtain the desired therapeutic effect. Hence, it is necessary to ensure that the drug is well absorbed by the body and produces the desired clinical outcomes [107]. The chemical composition of several ophthalmic formulations, such as moxifloxacin ophthalmic solution (0.5 % w/v) or ciprofloxacin antibiotics, has resulted in fundamental problems, including limited ability to penetrate tissues, short duration of stay in tissues, and/or quick breakdown of the drug molecules [108].

In addition to the above stated challenges, there have been several reports of adverse effects caused by certain ocular drug formulations. For example, Acyclovir 3 % ocular ointment (Zovirax) has been associated with blurred vision [109]. Other drugs, such as Restasis eye drops containing 0.05 % cyclosporine have been accompanying eye irritation, burning, redness, and aching sensations [110,111]. Overuse and repeated exposure of ocular tissue to steroid drugs can lead to local undesirable reactions including cataracts, increase in IOP and glaucoma. Moreover, the systemic cyclosporine absorption followed by topical administration might cause a systemic toxic effect such as kidney-related hypertension [112]. Ideally, to overcome the aforesaid drawbacks; nanomaterials with some physiochemical properties such as biocompatibility (lack of toxicity), stability inside a living organism, and the capacity to be sterilized are recruited. Moreover, the nanomaterials should provide better pharmacological benefits compared to traditional drugs, such as prolonged release, targeted administration, and improved penetration at the cellular level. The following properties of materials must be considered when designing nanomedicine for glaucoma treatment.

### 4.1. Biocompatibility

Biocompatibility is a crucial factor to be considered before using a material as a nanocarrier for development of nanomedicine [24,113]. The harmful effect of nanomaterials on living tissues may occur via many processes, including the production of oxidative stress as well as cell membranes disruption [114]. The materials used in the development of nanocarrier or nanomedicine should be biocompatible inside the body without activating inflammatory responses or cellular toxicities [115]. Several *in-vitro* and *in-vivo* tests, such as platelet aggregation, macrophage absorption, assessment of cell shape and viability, evaluation of clinical signs, examination of gross histopathology have been proposed to assess the toxicity of nanomedicine [116]. However, there are various types of transporters on human cells surface, and a significant difference between healthy and disease microenvironment. After the materials are applied to the eyes, it is difficult to accurately determine their specific behavior and impact as comprehensive safety evaluation of nanocarriers remain inadequate [28,117].

The major factors influencing the biocompatibility of nanocarriers are their physicochemical characteristics, namely including size, surface morphology, charge, and surface chemical groups [118]. For example, noncarriers with strong positive surface charges have potential to destroy the negatively charged cell membrane of mammalian cells [119]. Nanocarriers with a smaller size often have a greater ability to enter the cell membrane, resulting in increased toxicity to cells or tissues. For example, silica NPs with particle size of 15 nm demonstrated higher *in-vitro* and *in-vivo* retinal cytotoxicity compared to bigger size (50 nm) silica NPs [120]. However, properties of nanocarriers that might have *in-vivo* negative effects are often makes these nanocarriers as an attractive drug carrier [121]. For instance, cationic and/or small size nanocarriers have superior capacities of disrupting the lipid bilayer of cell membrane result in an enhanced interaction between cargo drug and desired tissues at cellular level [122,123]. Hence, the balance between the potential negative effects and desired capabilities of nanocarriers should be addressed when designing nanomedicine for glaucoma therapy.

### 4.2. Physical stabilization

Ideal nanocarrier or nanomedicine should have enhanced colloidal stability after being injected or installed in living tissues. For example, NPs are the most widely used drug nanocarriers. Smaller size NPs actively formed aggregates *in-vivo* due to thermodynamic instability [24,121]. The aggregation of NPs might cause a very high drug concentration due to accumulation of NPs at certain undesirable sites. In addition, NPs also interact with plasma proteins inside the body [121]. Therefore, care must be taken when injecting NPs via intravitreal route, because it may lead to disruption of the blood-retina barrier. Currently, both transmission electron microscope (TEM) and scanning electron microscope (SEM) is frequently used to monitor the biodistribution and surface morphology of nanomedicine inside the body [124]. In addition, fluorescence microscopy is also a feasible alternative for monitoring the fluorescent-tagged nanocarriers [125]. However, the above-mentioned strategies could only provide a general overview. There is a significant lack of understanding about the precise behavior of nanocarriers inside the intraocular environment, particularly in terms of their biodegradation and elimination from eye [24,126].

### 4.3. Proper sterilization techniques

Before *in-vivo* administration, the assembled nanomedicine should be sterilized, regardless of the materials utilized to carry the payload drug. However, an appropriate and applied sterilization strategies have become a limiting when developing nanocarriers as various sterilization techniques have been reported to change the physiochemical properties of nanocarrier materials and therapeutic agents [24,127]. Autoclaving, gamma irradiation and ethylene oxide are the most frequently used sterilization techniques for medical devices and pharmaceutical products [128]. In autoclaving sterilization technique, high pressure and temperature usually leading to physical instability of polymeric materials used in fabrication of nanomedicine [24,129]. Gamma irradiation has shown sterilization efficacy with some nanomaterials, however the generation of free radicals during irradiation process can caused physical instability and structural changes, particularly when the payload is a protein [130,131]. In addition, accelerated drug release was also observed from the nanomaterials after gamma irradiation [132,133].

Filtration and ultraviolet (UV) light are also most economical and commonly used sterilization techniques [134]. Filtration is a practical method using sterile filter with pore size of 0.20–0.22 μm which expel the contaminants without effecting the physicochemical characteristics of nanocarriers [135,136]. However, this sterilization technique may not be appropriate for larger size NPs which might be trapped inside the membrane [24]. On the other hand, UV light may cause the increased wettability of polymers. It is also important to note that addition of antimicrobial drug to the nanocarriers can be also very risky [2]. Nanomedicines are typically intended to continually release the payload drugs in eye for extended period of time. Therefore, long-term use of antimicrobial drug such as benzalkonium chloride inducing serious side effects. In short, there is no ideal sterilization technique for all nanomaterials [137]. Using different sterilization strategies for different ingredients separately and carrying out the whole manufacturing process

under sterilized conditions might be a practical approach [2]. The validation of the sterilization technique should be conducted on a case-to-case basis.

### 4.4. Controlled drug release profiles

Nanosystem with a controlled drug release profile is indispensable in glaucoma treatment to overcome the limitation of conventional eye drops which need frequent administration with repeated doses [113,138]. In addition, eye drops distribute medication to the eye in a frequent and pulsating manner, characterized by a peak concentration of the medicine followed by a decrease before the next dosage is given on the same day or the next day [139,140]. Due to the fluctuating drug concentrations or pharmacokinetics, the effects of the medicine might vary over time. This variability could lead to increased intraocular pressure at various times of the day, depending on the specific drug being given. An improved option might be the implementation of continuous medication administration, which would result in a persistent reduction of IOP [141]. Besides constant IOP reduction, controlled drug release from the nanoplatform has the potential advantage of reducing the total dose and also lowered or slow down the systemic exposure, which decreases the systemic side effects [3,140,142]. Controlled and sustained delivery of drug can be achieved by various nanocarrier systems including nanoparticles, nanofibers insert and nanogels or their combination. Nanosystems are typically prepared from carrier materials in the form composite nanodrug delivery systems.

The composite nanodrug delivery systems may be categorized into two types: matrix and reservoir nanodrug delivery systems [143]. In a reservoir-type nanodrug delivery system, the drug is contained inside a central core and is surrounded by membranes that are impermeable or have limited permeability. These membranes regulate the rate at which the drug is released [144]. In matrix-type nanodrug delivery systems, the drug is uniformly distributed inside the delivery system using a carrier material. Reservoir type nanosystems are usually designed to deliver the drug at a constant rate throughout the lifespan of the delivery system. On the other hand, matrix type nanosystems release the drug at a decreasing rate over time. However, the release rates might vary from the general patterns indicated before, depending on the design and manufacture of the delivery system [3,121]. An ideal medication delivery method for treating glaucoma would be a zero-order sustained release device. This technique will provide consistent drug concentrations for about 4 months or more in close proximity to the specific tissue location, allowing for sustained suppression of IOP once a single dosage is administered [138]. A further characteristic of an optimal delivery system would be its ability to deliver drugs to specific ocular tissues without the need for invasive eye surgery or injections, while maintaining a high level of effectiveness and a low safety risk.

### 4.5. Prolonged ocular residence

Prolonging the ocular residence time of antiglaucoma nanomedicine is crucial for enhancing their therapeutic efficacy. To increase absorption of ocular drug without rupturing the ocular epithelium, antiglaucoma nanomedicine should hold as much high concentration of drug in interaction with the ocular tissue for extended time period [3,145]. There are several strategies to achieve this goal. One approach is to modify the nanocarrier to increase their mucoadhesive properties by incorporating polymers such as chitosan or hyaluronic acid, which can interact with mucin in the ocular surface, thereby enhancing retention [146]. Another strategy is to formulate the nanocarriers system in the form of a gel or a viscous solution. These formulations can increase the interaction time of the NPs with the ocular surface, allowing for better penetration and sustained release of the antiglaucoma medication [147]. Furthermore, the size and surface charge of the NPs play a significant role in determining their residence time. By optimizing these parameters, it is possible to design nanocarriers that can stick to ocular surface and exhibit prolonged retention. In addition to formulation strategies, the method of administration also influences the residence time of antiglaucoma nanodrug. Techniques such as viscosity-enhancing agents, in situ gel formation, or ophthalmic inserts can all help in prolonging the contact time of nanoparticles with the eye. Lastly, the use of mucoadhesive polymers can further enhance the retention of antiglaucoma nanoparticles on the ocular surface [148]. By combining these various strategies, it is possible to design nanoparticles that exhibit prolonged preocular residence time, leading to improved therapeutic outcomes for glaucoma patients.

### 4.6. Higher corneal penetration

Despite of the prolonged ocular retention, it is still essential to discovered an effective strategy to improve the corneal permeability of antiglaucoma drugs enhanced the therapeutic efficacy. Small and positively charged nanocarriers may be beneficial as a penetration or permeability enhancers for ophthalmic drug delivery [97,149]. Due to their small sizes and easy surface functionalization, various nanocarrier such as a liposome, polymer micelles, dendrimers, nanogels, and nanocapsules, as well as some inorganic NPs such as quantum dots and mesoporous silica NPs etc., demonstrating great potential for enhancing the corneal permeability [150–153]. Baba et al., reported that NPs of hydrolyzable dye (200 nm) attained a greater (about 50-fold) ocular penetration compared to micron-sized particles as small size allows them to penetrate through the tight junction of the corneal epithelium [154]. In contrast, larger size nanoparticles may have difficulty crossing the tight junctions between corneal epithelial cells.

In addition, positively charged nanocarriers have both extended preocular retention time and enhanced corneal permeation due to inherent affinity of phospholipid component of cornea, however, care should be taken owing to potential eye irritation [155]. For instance, Wang et al. developed a PAMAM dendrimer nanogel to transport brimonidine and timolol, the two commonly used antiglaucoma medicines, for topical administration [148]. The use of this dendrimer nanogel resulted in a 17-fold enhancement in ocular permeability compared to the free drugs solution.

### 4.7. Target-specific delivery

The ocular drug delivery via nanocarriers must have target-specificity to minimize the off-target side effects [156]. Precise and target-specific delivery can be attained by active and passive methods. The active methods involved nanocarriers surface functionalization or coatings with a ligand molecule, such as coating with RBC membranes (natural cell membrane) to upsurge circulation time, cell attaching, and cell uptake, functionalization or conjugation with proteins, polysaccharide and hybridized DNA, such as albumin, hyaluronic acid, chondroitin sulfate and antibodies for strong affinity and avoiding opsonization, on the other hand, passive method involved carefully choosing the nanocarrier type such as liposomes have inherent higher penetration capacity or using permeability enhancer agents [103,157].

## 5. Factor effecting nanomedicine in glaucoma treatment

Nanomedicines are increasingly being explored to enhance the bioavailability of cargo drug at the target sites with lower dose and show sustained and continuous drug release with no systemic toxicity [33,34], overcoming the obstacles in conventional drug delivery. Generally, the *in vivo* performance of nanomedicine e.g., biodistribution and pharmacokinetics can be influenced by many factors, such as particle size/-diameter, surface charge, solubility, absorption, and degradation proficiency of the nanomedicine inside the eye [158,159]. A myriad of efforts has been devoted in the previous few decades to optimize the above-mentioned multiple factors for prolonging the bioavailability, enhancing the biodistribution and minimizing the possible systemic

toxicity.

The successful and appropriate drugs encapsulation during the nano-assembly of nanomedicine is the foremost factor need to be considered carefully to ensure the therapeutic efficacy of synthesized nanomedicine. First, the choice of nanocarrier materials, such as lipids or polymers, which can influence the drug encapsulation capacity, release kinetics and stability. Secondly, the nature of drug also impacts the drugs encapsulation during the nano-assembly of nanomedicine [160]. For example, highly polar water-soluble drugs are entrapped within the aqueous compartment of the liposomes. Thus, their encapsulation efficiencies will be governed largely by the fraction of the total solvent which is 'pinched off' or entrapped during liposome formation. In contrast, less polar hydrophobic drugs may bind to or intercalate to the liposome membrane; generally, these drugs tend to be incorporated more efficiently in fluid' membranes where the fatty acyl side chains have considerable freedom of movement. In contrast, the encapsulation efficiencies of polar drugs are relatively independent of the nature of the liposome membrane as the membrane provides an adequate permeability barrier. Hydrophobic drugs, because of their direct interactions with the liposome membrane, are likely to change the physical characteristics of liposomes when present in large amounts. Additionally, the method of nano-assembly, whether it be self-assembly, desolvation, coacervation, spray drying and microfluidics, can influence the uniformity and reproducibility of the encapsulation process. Overall, a complete understanding of these factors is essential for designing nano-assembly systems that efficiently encapsulate drugs and facilitate their controlled release at the desired site.

For therapeutic efficacy, the size/diameter of nanomedicine is a crucial parameter as it affects their penetration through ocular tissues and barriers [161]. Nanomedicine with larger particle size/diameter typically has greater drug loading capability and extended drug release [145,146,162,163]. However, nanomedicine in the form of nanosuspension, massive use of large particle size subjects leads to poor injectability, due to the clumping of large particles in needle and causes backflow of injected suspension from the site of injection. In addition, larger size NPs show low cellular uptake compared to smaller ones as the Brownian movement of larger size NPs decreases [2]. For nanomedicine as an ocular nanofiber insert, larger-diameter nanofibers require more access with serious invasiveness for proper administration. On one hand, nanomedicine with smaller particle size/diameter can potentially reach intraocular targets more effectively but nanomedicine with too small size/diameter (<10 nm) suffer with low drug loading capacity, fast drug release and rapid *in vivo* elimination due to intraocular pressure [62]. In short, an appropriate balance among the size/diameter, drug loading capacity and the feasibility of administration when designing a nanomedicine for glaucoma treatment. The surface charge of nanomedicine also plays a vital role in ocular delivery for treating glaucoma. The surface charge of nanoparticles can significantly impact their delivery to anterior and posterior segments of eye, cellular uptake and internal cells trafficking [164]. For example, both the conjunctiva and cornea have negative surface charges, hence retention time of cationic nanoparticles can be enhanced more evidently on negatively charged ocular tissues compared to anionic ones, providing an increased opportunity for the drug to enter the eye. The lens capsule embraces collagens, laminins, and proteoglycans with a negative charge, hampering the entrance of positively charged nanomedicine, while neutral nanocarriers were actively diffused across the lens capsule compared to anionic ones. In sclera, nanomedicine with positively charged surface appear to be permeate-hindered, probably due to their electrostatic interaction with the negatively charged proteoglycans in the scleral matrix [156]. In posterior segment, the surface charges of the nanomedicine influence the vitreal dispersion as well as retinal bioavailability of cargo drug. The net negative charge of the vitreous humor modulates the diffusion of nanomedicine. So, negatively charged nanomedicine freely diffuse through the vitreous humor, while positively charged nanomedicine get trapped [101].

In addition, the positively charged and neutral nanoparticles, for example, are more likely to interact with negatively charged cell membranes, potentially enhancing cellular uptake and are more probably to penetrate through the retina and subsequently improving drug delivery efficiency [165,166]. However, nanoparticles with too positive surface charges may damage the cell membrane and cause toxicity [119,167]. On the other hand, negatively charged nanocarriers may have better stability and reduced interaction with the ocular surface as cell membrane exhibit slightly negative charge, but they could also have lower cellular internalization rates owing to the repulsive forces [168]. It is important to carefully consider the surface charge of nanomedicine in glaucoma treatment to the delivery efficiency, minimize potential adverse effects, and enhance therapeutic outcomes.

Understanding of interactions between cell surface and nanocarrier system is essential to unravel the cellular uptake and its internalization mechanism. However, the precise mechanism underlying the cellular uptake process of nanomedicine remains a major problem, due to the expression of over hundreds of transporters on cells surface as well as the cell membrane dynamic fluidity [169]. It is possible for distinct nanomedicine to interact differently with the same type of cell lines when they are absorbed at various times or in different microenvironments. Among different internalization mechanisms, endocytosis including phagocytosis, micropinocytosis, and receptor-facilitated endocytosis is most likely involved in the internalization of nanomedicine. The feasibility of each mechanism varies depending on factors such cell type, the size of NPs, and the presence of receptors on cell surfaces [170,171].

Apart from size and surface charges, the shape of nanoparticles plays a promising role in the bio-performance of nanomedicine. For example, sphere-shaped mesoporous silica NPs (MSNs) actively eliminated compared to rod shape (nanorods) by renal excretion [172]. In addition, other surface properties, such as hydrophobicity, stiffness, topography also played a vital role in adhesion of nanocarriers with cell surface, which may also influence the biocompatibility and internalization mechanism of nanomedicine [173,174]. Several organic and inorganic coating materials have been studied to alter the interface between nanomedicine and cells and enhance their biosafety, considering the significance of biocompatibility [175]. Typically, natural biomaterials like PLGA, HA, and PEG have superior biocompatibility. Therefore, natural biomaterials have been used to modify the surface of other nanocarriers in order to improve their biocompatibility and reduced the undesired effects [176,177]. Furthermore, the application of suitable surface modification may enhance the duration of drug residence on the ocular surfaces and enhance the penetration of cargo drug. In addition, the conjugation of appropriate ligands or aptamers on the surface of nanomedicine might enhance particular targeting and enable precise treatment.

## 6. Nanocarriers in designing of nanomedicine

Nanocarriers are unique particulate drug delivery devices characterized by their nanometer-sized particles (ranging from 10 to 1000 nm) and particular surface charge. The presence of surface charge enhances the colloidal stability of these particles, as well as their capacity for surface conjugation and remain intact at specific sites. For instance, particles with same surface charges repel each other due to repulsive forces which prevent the aggregation or agglomeration of particles. In case of ocular delivery, conjunctiva and cornea exhibited negative surface charges, thus showing strong affinity for cationic nanocarriers due to electrostatic interaction leading to enhanced retention at ocular surface such as cornea and facilitated topical delivery to anterior region of eye. In contrast, anionic nanocarriers actively diffuses to retina upon intravitreal administration. Nanocarriers with small particles size and surface charges have the capacity to deliver the therapeutic molecules to desired site by combating the ocular barriers [16,178]. Different types of nanocarriers with delivery routes are summarized in Fig. 4.

Nanocarriers such as liposomes, nanoparticles, lipid nanoparticles,

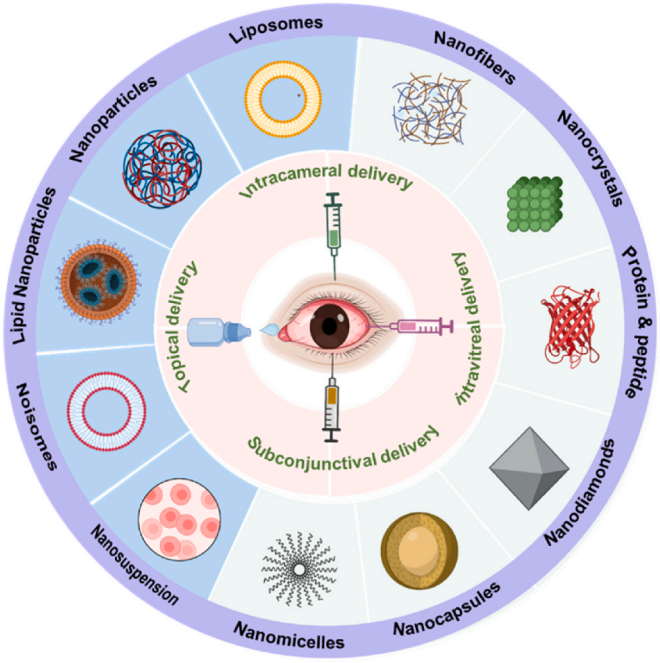


**Fig. 4.** Schematic illustration of different nanocarriers used in the development of nanomedicine for glaucoma treatment and their possible routes of administration.

noisome, nanosuspensions, polymeric nanomicelles, nanodiamonds, nanocapsules, nanospheres, protein/peptide nanoparticles nanocrystals and polymeric nanofibers have been investigated for the development of nanomedicine in glaucoma treatment. The respective generalized advantages and disadvantages of the above-stated nanocarriers have been summarized in Table 3.

### 6.1. Liposomes

Liposomes are spherical structures made of lipid materials, either synthetic or natural, that consist of an inner aqueous core surrounded by phospholipids bilayers. Liposomes may vary in size from nanometer-to micrometer scale [179]. The presence of a lipid outer layer allows liposomes to possess both excellent ocular penetration and adequate biocompatibility, biodegradability, and human safety. These characteristics have contributed to the recognition of liposomes as the first nanomedicines authorized by the FDA [180]. Furthermore, liposomes have the potential to load hydrophilic and lipophilic drug concurrently, due to the distinct compositions of their inner and exterior structures which enhances the bioavailability of drug at the target site via simultaneous drug delivery [178]. Various attempts have been made with liposomes to prolonged their preocular residence time, improve corneal permeation, controlled drug delivery for bioavailability enhancement.

**Table 3**
Comparative advantages of nanomedicine-based drug delivery in respect to conventional ocular drug delivery for glaucoma treatment.

| Nanomedicine-based ocular drug delivery | Conventional ocular drug delivery |
|---|---|
| Enhanced aqueous solubility | Restricted aqueous solubility |
| Enhanced corneal permeability | Limited corneal permeability |
| Sustained/extend therapeutic effects | Immediate/shorter therapeutic effects |
| Target-specific delivery | Nonspecific delivery |
| Improved bioavailability | Low bioavailability |
| Abated intrasubject variability | Intrasubject variability |
| Low doses and reduce frequency | High doses and repeated administration |
| Improved therapeutic efficacy | Limited therapeutic efficacy |
| Minimized possibility of adverse effects | Possibility of adverse side effects |
| High patient compliance | Patient incompliance |

Fahmy et al., developed liposomes encapsulated with thymoquinone and latanoprost and injected via subconjunctival route for glaucoma treatment [181]. The prepared liposomes showed a diameter of 200 nm with enhanced drug encapsulation efficiency of about 88 %. Furthermore, the drug loaded liposomes exhibited prolonged and continuous drug release up to 84 h and significantly reduced the IOP compared to free drugs. Recently, some pre-clinical studies have studied the safety and efficacy of drug-entrapped nanoliposomes in glaucoma therapy. Dorzolamide (DRZ)-entrapped nanoliposome showed better IOP reduction efficacy in rabbit model as compared to DRZ marketed formulation [182]. The IOP lowering capacity of DRZ-entrapped nanoliposome group (23.26 ± 9.24 % and 9.25 ± 5.76 %) and DRZ marketed formulation group (32.60 ± 7.90 %, and 17.48 ± 7.62 %) was observed for two weeks.

Surface functionalization of liposomes with ligand can provide target-specific delivery with enhanced bioavailability. Jin et al., reported that brinzolamide (BRZ) loaded nanoliposomes functionalized with D-alpha tocopherol (Vitamin E) significantly reduced the IOP without causing any damage to cornea [99]. The vitamin E surface functionalized liposomes exhibited controlled and sustained drug release, prolonged preocular retention, improved corneal permeation and significantly lowered the IOP without toxicity to ocular tissue compared to BRZ nanoliposomes and commercially available BRZ suspension (AZOPT®). In a recent study, a dendritic oligoethylenimine functionalized liposome was developed for simultaneous delivery of dual antiglaucoma drugs, timolol and latanoprost [183]. The prepared liposomal formulation (TLPL) exhibited an extended precorneal retention time. Furthermore, TLPL presents augmented cellular uptake and higher opening capacity of tight junctions, contributing subsequently to the paracellular and transcellular permeation, thus improving the trans-corneal delivery (Fig. 5). The dual-drug-loaded liposomal formulation showed a sustained and effective IOP reduction for 5 days, following topical single dose administration as an eye drop in Norway brown rats, without causing any ocular discomfort, irritation and tissue damage.

### 6.2. Nanoparticles

Nanoparticles (NPs) are round-shaped colloidal dispersion with diameter ranges from 1 to 1000 nm, constructed by several materials including polymers, organic materials, inorganic materials, peptides, proteins and small amphiphilic molecules [56,178]. The therapeutic performance of NPs depends on various physicochemical properties such as size, surface charges, shape, solubility and stability. Recently, NPs have become a hotspot among nanocarriers used in ocular therapy due to the miscellany of materials been exploited for their preparation, including various polymers such as poly(ε-caprolactone) (PCL), poly (lacticco-glycolic acid) (PLGA), CH, chondroitin sulfate (CS), hyaluronic acid (HA) and gelatin. Besides, other common inorganic materials such as silver, gold, silica, Znic oxide, and cerium oxide have been employed to prepare NPs [2]. On the basis of preparation materials, NPs are broadly classified into polymeric NPs, inorganic NPs and biocatalytic nanoreactors.

#### 6.2.1. Polymeric NPs

Polymeric NPs are most stable and spherical shaped NPs with nanoscale size (1–1000 nm) that can easily diffuse through the biological membrane act as a barrier system, and actively deliver the payloads to the target site. NPs with smaller size exhibited large surface area, and an enhanced the drug entrapment ability [184]. Polymeric NPs categorized into three generation (Fig. 6A). First-generation polymeric NPs are simply composed of polymer matrix or core. Second-generation polymeric NPs include NPs with polymeric coating or shell. This polymeric coating or shell can improve the adhesion of NPs to target or disease site. The third-generation NPs are legend-conjugated polymeric NPs, which can actively bind to specific cells or tissue and precisely release the cargo

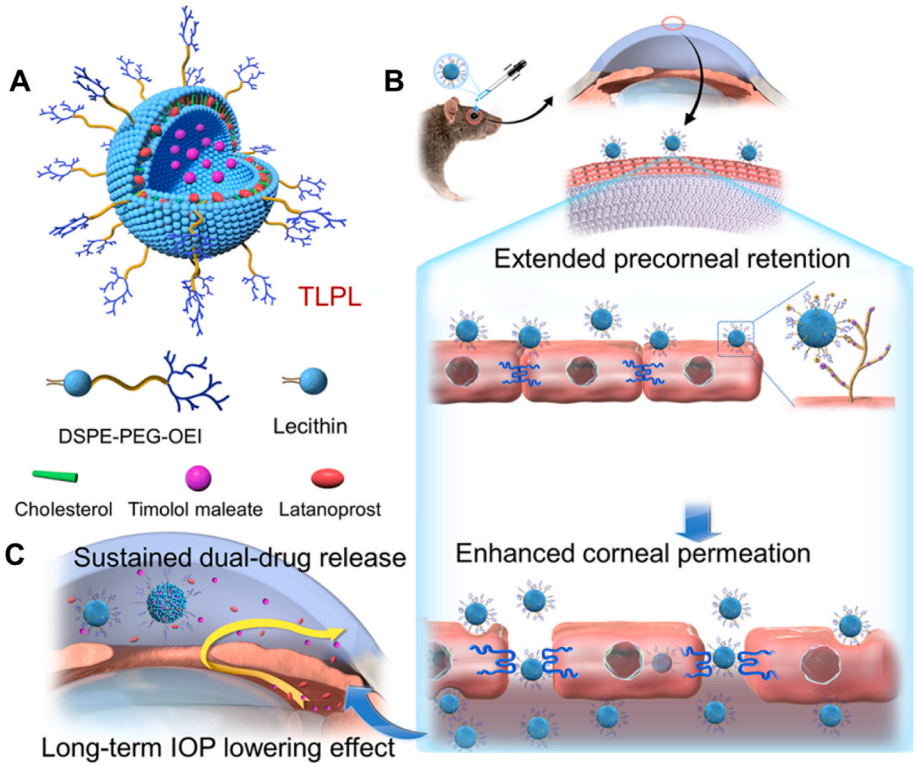


**Fig. 5.** Illustration of (A) TLPL liposomal formulation structure. (B) *In-vivo* mechanisms of improving the ocular absorption. (C) Prolonged and sustained dual drug release for long term IOP reduction. Reproduced from Ref. [183] with permission from ACS.

drug at target site [16]. For example, propoxylated glyceryl triacylate (PGT) NPs of timolol (1:1 ratio) showed a sustained release of timolol for extended period [185]. Moreover, poly(butyl)-cyano acrylate NPs with pilocarpine can significantly reduce the IOP without any associated adverse effect [186]. Acetazolamide (ACZ) -loaded Eudragit NPs exhibited improved corneal permeability and enhanced flow through cornea as compared to conventional ACZ suspension in transcorneal permeation study. Besides, ACZ-loaded Eudragit NPs and ocular insert significantly reduced the IOP and enhanced the *in vivo* ocular tolerability as compared to conventional ACZ suspension [187]. Another *ex vivo* transcorneal permeability study demonstrated higher ACZ corneal penetration of 74.50 ± 2.20 mg/cm$^2$ at 8 h with NPs-in situ gel compared to corneal penetration of 20.08 ± 3.12 mg/cm$^2$ and 16.03 ± 2.14 mg/cm$^2$) for ACZ eye drops and ACZ suspension, respectively [188]. Additionally, ACZ-loaded NPs-in situ gel has no toxic effect on corneal tissue. Likewise, ACZ-loaded PLGA NPs in situ gel (1 %) exhibited better IOP-lowering potential 1 h after installation and last for 8 h, while ACZ eye drops (1 %) sustained their therapeutic effect for around 2 h in normotensive rabbits.

### 6.2.2. *Inorganic NPs*

While the above-mentioned soft polymeric NPs are skilled for carrying different types of therapeutic agents, inorganic NPs have inherent potentials that are fetched by their chemical and physical characteristics [56]. For instance, mesoporous silica NPs (MSNs) have shown considerable competence in drug delivery field due to their biodegradability, stability, large surface area, bigger pore volume, and modifiable pore diameter [189]. Particularly, MSNs could efficiently penetrate the cornea and reach to the disease site. Hu et al., prepared eye drops with SNP-loaded MSNs to continuously release NO in the trabecular meshwork and Schlemm's canal area [190]. The *in-vivo* model showed that the decrease in IOP lasted from 3 h to 48 h by using MSNs, with just 1/40th of the dosage of SNP solution. However, the researchers discovered possible harmful effects of SNP on the traditional outflow tissue. This is because using this NO donor for an extended period of time might lead to protein nitration [191]. Furthermore, the inclusion of magnesium hydroxide NPs led to improved capacity of hydrophilic antiglaucoma medicines to penetrate the cornea and reduce IOP [192].

Interestingly, some inorganic NPs work not just as drug carriers, but as the drugs themselves. Nanoceria particles consist of nanocrystalline cerium oxide ($CeO_2$), also referred to as ceria, which is a kind of rare earth oxide. Ceria NPs possess antioxidant, anti-inflammatory, and anti-angiogenic properties, making them an attractive candidate for neurotherapy [193]. Luo et al., recently prepared targeted hollow ceria NPs with pilocarpine for dual-functional glaucoma treatment [70]. A receptor antagonist (ZM241385) that precisely binds with ciliary body, CH, and PEG, was employed in the surface modification of ceria NPs (Fig. 6B). The formulation led to a 42-fold increase in the duration of effectiveness and a 250-fold increase in the amount of pilocarpine that was absorbed into the body after a single dose administration. Furthermore, in a rabbit model, the development of glaucoma was reduced, likely due to the ceria NPs' capacity to lower the production of ROS and inflammatory chemicals. Nevertheless, a significant issue related to inorganic NPs is their lack of biodegradation or efficient elimination from the human body. Hence, the cytotoxicity assessment and cumulative noxious effect of inorganic NPs is warranted.

### 6.2.3. *Biocatalytic nanoreactors*

Biocatalytic nanoreactors have been recently developed which increases the specificity and efficacy of nanomedicines. Typically, biocatalytic nanoreactors are enzymes containing vesicles which enable the conversion of inactive pharmaceuticals into active therapeutic agents in a specific area, instead of just transporting the drug molecules [195]. This enzymatic prodrug approach could enhance therapeutic efficacy while reducing the toxic side effects to the minimum level [196]. [120]. Chandrawati et al., developed a new method for delivering NO that specifically targets the TM [194]. This method allows for the controlled release of NO at varying doses by enzyme biocatalysis. This method

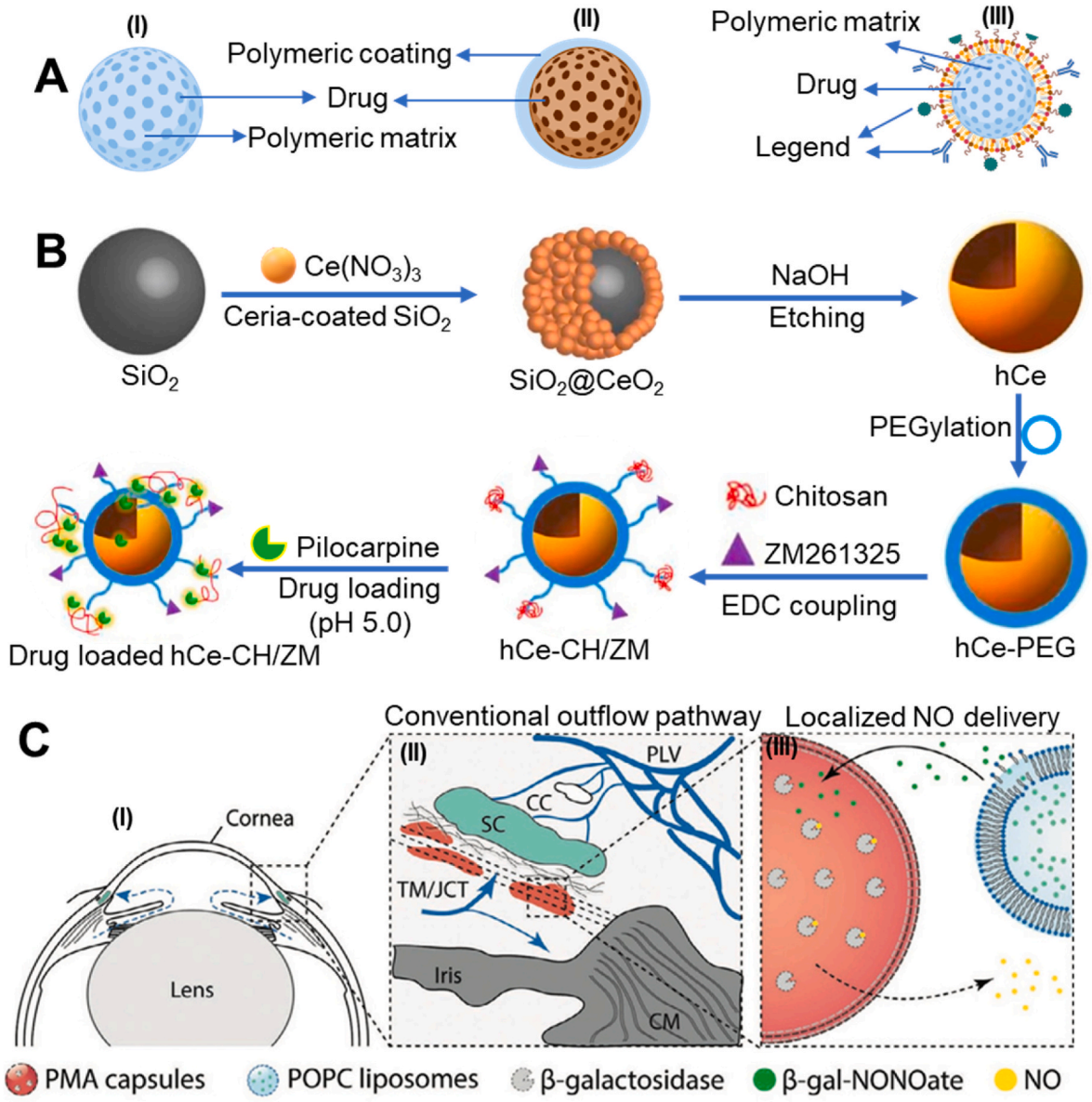


**Fig. 6.** (A) Different types of polymeric NPs. (I) Drug polymer matrix or core NPs (II) Polymer-coated or polymeric shell. (III) Legend or targeted molecule decorated polymer matrix or core NPs. (B) Synthesis of hollow ceria NPs (hCe NPs) via silica templating method followed by dual functionalization with CH/ZM241385 and loading with pilocarpine for glaucoma treatment use as an eyedrops. Reproduced from Ref. [70] with permission from Elsevier. (C) Localized delivery of NO via biocatalytic nanoreactor. (I) Conventional outflow of aqueous humor (blue-doted arrows). (II) Diagram of iridocorneal angle with close view. (III) On-site localized delivery of NO inside the TM, close to Schlemm's canal. Poly(methacrylic acid) (PMA) capsules entrapped β-Galactosidase starting a localized delivery of NO at the aqueous humor outflow resistance site upon liposomes degradation, which carried NO donors (β-gal-NONOate). CC: collector channels, CM: ciliary muscle, PLV: perilimbal vessels and JCT: juxtacanalicular connective tissue. Reproduced from Ref. [194] with permission from Elsevier.

consists of two main steps: first, the β-galactosidase-loaded LbL capsules are injected into the trabecular meshwork, where they get entangled (Fig. 6C). Then, liposomes containing β-galactoside NONOate, a prodrug that releases nitric oxide (NO), are delivered and come into contact with the capsules. The enzyme-loaded LbL capsules were localised in the outflow resistance areas of the trabecular meshwork via the traditional outflow channel due to their strong structural integrity. The diffusion of β-galactoside NONOate towards the capsules might lead to the generation of NO when the liposomes break down, due to the reduced distance for diffusion caused by the aqueous outflow. Furthermore, the necessary amount of NO may be achieved by altering the concentration of externally administered donors inside the liposomes [194]. Biocatalytic nanoreactors are expected to reduce tissue damage caused by nitration effect, in comparison to the continuous supply of an active NO donor alone.

### 6.3. *Lipid nanoparticles*

Lipid nanoparticles (LNPs) are rapidly developing DDS in ocular field and reflected as a most promising DDS in glaucoma treatment by improving the drawbacks in conventional treatment. Previously, topical liposomes were widely used lipid nanocarriers in both pre-clinical and clinical studies, effectively delivering the ophthalmic drugs to retina and vitreous [197]. LNPs are superior nanocarriers compared to polymeric NPs and liposomes in many aspects. For example, LNPs are formulated without using any organic solvents, which produce toxic degradation byproducts. As a result, LNPs show a very low systemic toxicity and stabilize as well as protect the payload drug from biodegradation, while exhibited a controlled and sustained drug release profile [197,198].

Lipid NPs are oil-in-water (O/W) emulsions comprised of lipid core surrounded by a shell or corona of water molecules stabilized with

amphiphilic surfactant. Hence, Lipid NPs are able to transport both lipophilic and hydrophilic drug molecules. Lipid might be easily transformed from liquid to solid state in various structures and dispersed in water solution at body or room temperature [199]. So, LNPs are the spherical vesicles of ionized lipids dispersed in aqueous dispersion and exhibited positive charge at the normal pH with a particle size from 40 to 1000 nm. LNPs can be categorized into two sub classes: solid lipid NPs as well as nanostructured lipid carriers (Fig. 7) [200].

### 6.3.1. Solid lipid NPs (SLNs)

SLNs are colloidal nanocarrier systems made of solid lipids dissipated in aqueous surfactant systems with particle size ranges from 10 to 500 nm [201]. SLNs were formulated to overcome the drawbacks of liposomes and polymeric NPs. SLNs are reflected as a more improvised form of nanocarriers deliver numerous advantages, such as enhanced drug loading efficiency, extended drug release, improved bioavailability, enhanced stability by protecting the drug molecules enzymatic degradation, better biosafety and cost-effectiveness ratio, especially for high-scale production [202,203]. Furthermore, SLNs increase the corneal permeation and conjunctival uptake, thus prolonged the retention period of cargo drug in both posterior and anterior eye segments [204]. Besides, SLNs also reduced the toxicity induced by the frequent administration of high doses. Li et al., prepared the cationic and anionic SLNs with tetrandrine for retinopathy and glaucoma treatment using emulsion evaporation solidification method [205]. The prepared SLNs showed a particles size of 15.29 ± 1.34 nm and 18.77 ± 1.23 nm with surface charges of 5.11 ± 1.03 mV and – 8.71 ± 1.23 mV for cationic and anionic SLNs, respectively. The anionic SLNs were efficiently internalized by cells with enhanced intra cellular drug concentration in human lens epithelial cells. This study has shown the enhanced diffusion potential of anionic SLNs into vitreous region with superior retinal penetration compared to cationic SLNs. Satyanarayana et al., improved the precorneal residence time of bimatoprost (BTP) by formulating SLNs for glaucoma treatment [206]. The optimized BTP-loaded SLNs was anionic in nature with surface charge of -9.96 ± 1.2 mV and exhibited an average particle size of 183.3 ± 13.3 nm. Furthermore, SLNs showed a sustained release of BTP for up to 12 h and admirable biosafety with no signs of corneal toxicity after treatment with BTP-loaded SLNs. In short, SLNs might represent a promising nanocarrier system for improving the corneal penetration and bioavailability of antiglaucoma drugs.

### 6.3.2. Nanostructured lipid carriers (NLCs)

NLCs have been explored as a next generation lipid-based nanocarriers system to compensate the eminent drawbacks of SLNs including hydrophobic drug loading ability, drug expulsion caused crystallization of lipids and translation of alpha to beta (α–β) confirmation of solid lipids upon storage. NLCs endorsed an amorphous solid matrix state at both room temperature and body temperature, resulting from the combination of both liquid and solid lipids. NLCs' physiological and biodegradable lipid composition contributes to their exceptional drug

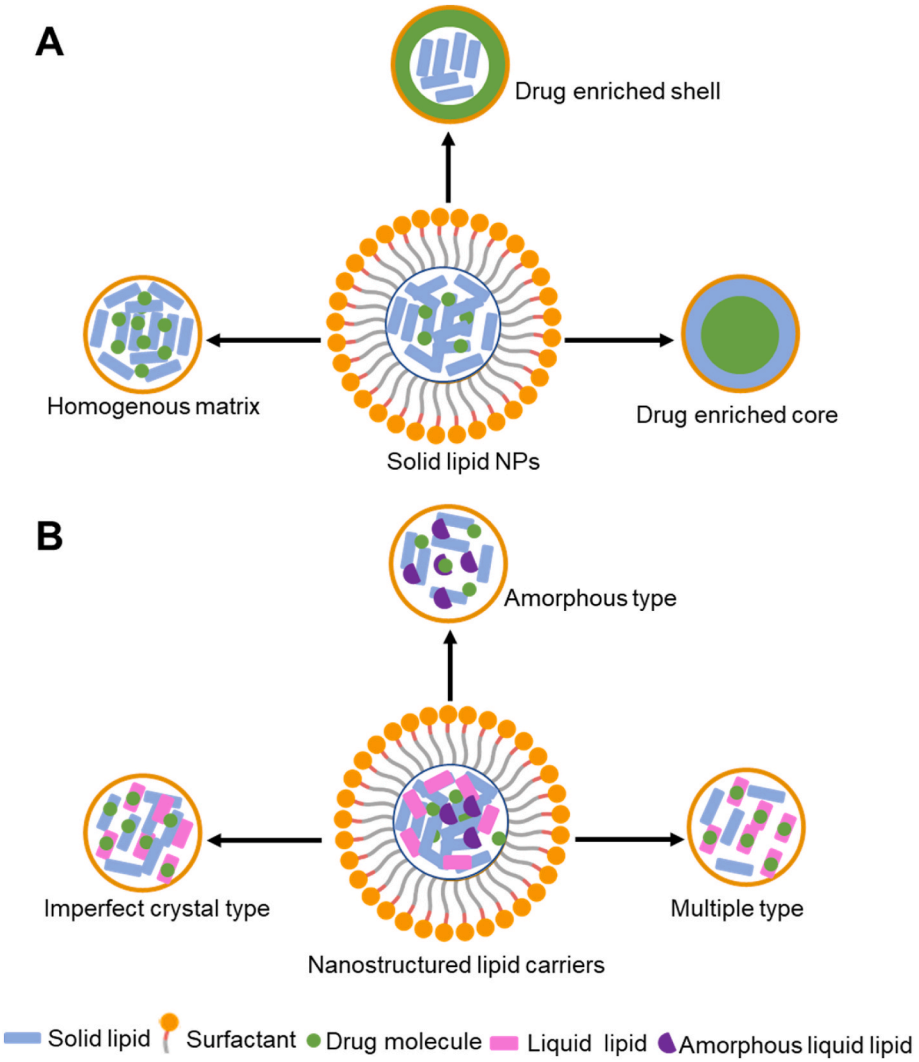


**Fig. 7.** Different types of lipid NPs. (A) Solid lipid NPs. (B) Nanostructured lipid carriers.

tolerance. Also, in comparison to SLNs, which contain both hydrophilic and lipophilic drug molecules, NLCs have a greater drug loading and an extended drug release duration [207–209].

In general, NLCs are categorized into non-shaped (amorphous), imperfect, and multiple-structured NLCs. The amorphous type NLCs do not have a regular or crystalline matrix, henceforth it averts premature drug expulsion. On other hand, the imperfect NLCs with perforated crystalline structure exhibited which provide space for the entry of lipophilic drugs into particles. Third one, multiple structures type NLCs comprises of several layers of liquid lipid embeded in a solid lipid matrix. This type NLCs were employed to evade the drug decomposition induced by the solid lipid. The NLCs based formulations have been demonstrated to actively transport the drug molecules to both anterior and posterior regions of eye [210]. For instance, Luo and co-authors described CH-coated NLCs with genistein formulation administered via topical route, which improved the transcorneal permeation and enhanced the bioavailability of cargo drug in aqueous humor of eye compared to the standard drug solution [211]. Moreover, triamcinolone acetonide loaded NLCs exhibited improved therapeutic efficiency in mice. The prepared NLCs was able to transport the cargo drug to posterior region of eye through non-corneal and corneal pathways after topical administration [212]. Hence, these reports suggested that the NLCs are good candidates in ocular drug delivery for glaucoma treatment.

### 6.4. Niosomes

Niosomes (Nios) are nonionic amphiphilic nanocarriers in the form of spherical, closed bilayer structures. Nios offer a viable drug delivery method that may be used in combination treatment regimens since they may transport hydrophilic and hydrophobic drugs simultaneously [213]. Nios have favorable therapeutic responses and prolonged half-life to improve bioavailability with reduce drug doses. However, the main advantage of Nios is the use of nonionic surfactants of non-toxic nature [214]. Timolol maleate (TM)-loaded Nios using CH have revealed an extended effect in lowering the IOP by releasing timolol in a sustained pattern for longer period [215]. In glaucoma rabbits' model, TM Nios coated with CH reduced the IOP for longer time over 8 h compared to conventional dosage form effective only for 2 h ACZ loaded Nios show improved and extended drug release after installation in eye, which can overcome the limitation of oral drug [216]. In addition, multilamellar Nios, can encapsulate a higher concentration of drug molecules and exhibited prolonged and continuous drug release.

### 6.5. Nanosuspension

Nanosuspension (NSP) is a colloidal nanocarrier system, in which solid particles dispersed in a liquid medium usually prepared by high-pressure homogenization or/and various other milling methods [217]. NSP could be easily combined with other DDs (hydrogels) due to its hydrophobic or non-water-soluble nature. NSP are specially designed for effective delivery of hydrophobic drugs, to enhanced their bioavailability [218]. For instance, in situ gel-forming NSP of coleonol (forskolin) significantly lowered the IOP (31 %) with a prolonged drug efficacy for about12 h, compared to other conventional DDS [219].

Drug molecules after entering the body encounter several ions via electrostatic interactions which reduces the drug molecules stability. To overcome this, polymers like Ion Exchange Resins (IERs) with substituted basic groups (quaternary ammonium group) for anion exchangers or acidic groups (sulfonic or carboxylic groups) for cation exchangers are employed. IERs actively protect the ionic drugs via shielding effect. Betaxolol-loaded NPs using IERs complex suspension (Betoptic S) have been commercially available as ophthalmic DDS. The betaxolol loaded cationic exchange resin provides microscopic beads with diameter of 5 μm and its cul-de-sac residence time could increase with help of polyacrylic polymer [220]. In parallel study, patients with ocular hypertension or primary open-angle glaucoma, no substantial difference was observed between betaxolol solution (0.5 %) and Betoptic S (0.25 %) in IOP reduction, however prevalence of ocular comfort after administration was significantly higher for Betoptic S [221]. Hence, NSP will be a promising DDS for water in-soluble anti-glaucoma drugs (carbonic anhydrase inhibitors) in future.

### 6.6. Polymeric nanomicelles

Polymeric nanomicelles (NMs) are spherical amphoteric structures comprised of amphiphilic polymers with hydrophilic and lipophilic parts. The amphiphilic polymers self-assembled in aqueous solution to form micelles, in which lipophilic tail assembled to from the micelle core while hydrophilic head forms the shell or corona. Various crucial factors such as polymer composition, site of action, drug loading, nanomicelle-tissue interaction, drug release rate, surface charges and size need to be considered when designing a nanomicellar formulation [28,222,223]. Hydrophobic or water insoluble drug encapsulated into the core of micelle via active or remote loading depending on the adopted method of preparation. The drug loading process involves hydrogen bonding or/and hydrophobic interactions between the polymer and cargo drug molecule. NMs could be prepared by either direct dissolution, film hydration, solvent evaporation and dialysis method. The micelle core drug encapsulation efficiency mainly depends on preparation method of micelles and degree of polymer-drug interactions.

In general, preparation methods like film hydration and solvent evaporation result in higher drug encapsulation efficiency compared to dialysis and direct dissolution methods. Furthermore, higher drug encapsulation efficiency might be achieved by increasing the concentration of amphiphilic polymers. Polymeric NMs exhibited a low critical micelle concentration (CMC) and higher stability [224]. The ocular adhesion of NMs could be enhanced by conjugating with mucin-targeting molecules such as phenylboronic acid and cyclic peptide ligand. Further, the shrinking of NMs has also shown to upsurge their efficacy, however premature degradation and drug release in systemic circulation remains an obstacle to clinical translation of NMs. Crosslinking of NMs could enhance the systemic stability to circumvent the premature degradation and drug release and allow stimuli-responsive drug release after topical ocular installation [225,226]. NMs not only enhanced the corneal permeability but also employed to target the posterior region of the eye. Chitosan oligosaccharide-valylvaline-stearic acid NMs demonstrated the enhanced *in vivo* efficacy by targeting the posterior regions after conjunctival injection [227].

### 6.7. Nanocapsules

Nanocapsules are polymeric nanocarriers in which drug molecules entrapped inside a matrix or surrounded by protective membrane with diameter of $\geq$10 nm. The drug molecules adsorbed, entrapped or dissolved in the polymeric matrix [228]. Nanocapsules gained a considerable attention as a nanocarrier in the designing of ocular nanodrug delivery system. The entrapment of drug molecule in core surrounded by protective polymeric coating allow nanocapsules to infuse the ocular's barriers efficiently and reach the disease site. This enhances the residence time of cargo drug in the eye which subsequently improved the bioavailability and therapeutic efficacy. Due to the versatile nature, nanocapsules has been successful employed in the delivery of several therapeutic agents, such as anti-inflammatory, anticancer and anti-glaucoma drugs [229]. Nanocapsules distinctly decrease the drug doses required to attain maximum therapeutic responses.

The transport of the drug molecule via nanocarriers to the disease sites at a reduced dose evades numerous side effects and improved the intended therapeutic efficiency. Lee et al. used poly (ε-caprolactone) (PCL) nanocapsule carriers to produce a novel nanoformulation of pilocarpine (PILO PCL NC) with sustained release. The cargo drug

pilocarpine is reported to be released from the capsular barrier over a duration of 42 days [144]. PILO PCL NC has almost three times greater pilocarpine loading efficiency compared to pilocarpine loaded poly ε-caprolactone nanospheres. Additionally, it demonstrates a sustained pattern of drug release when evaluated *in vivo*. In addition, PILO PCL NC demonstrated a sustained impact in reducing pressure-induced damage in the retina and cornea of the eye. The gel-like nature of the formulation enhances its adhesive properties, resulting in increased contact time with the cornea and improved absorption and bioavailability of pilocarpine.

### 6.8. Nanodiamonds

Nanodiamonds (NDs) are carbon nanoparticles with a diameter ranges from 2 to 10 nm exhibited truncated octahedral structure. NDs have customized surface structure and can be functionalized with innumerable ligands or functional groups via covalent or non-covalent bonds [230]. NDs have significant application in ocular drug delivery for the management of ocular diseases such as glaucoma. In a pre-clinical study, lysozyme-stimulated release of timolol maleate (TM) loaded NDs and further embedding NDs in contact lenses. During preparation, first individual NDs were coated with cationic polymer polyethyleneimine (PEI) and afterward cross-linked with chitosan an enzyme sensitive polysaccharide, forming a NDs nanogel encapsulated with TM. Hence, the sustained and controlled release of TM could be achieved when an enzyme (lysozyme) dissociates the chitosan in NDs nanogel. In addition, NDs also provided a mechanical support to contact lens [16].

### 6.9. Proteins/peptide nanoparticles

The use of protein/peptide based nanocarrier systems seem very promising since they are non-toxic, biodegradable and have no antigenic activity. Various proteins/peptides such as albumin, elastin, gelatin and elastin-like recombinamers etc. have been used for development of ocular delivery systems [231]. Kim et al. prepared human serum albumin loaded with brimonidine (HSA-Br-NPs) for glaucoma treatment [232]. The administration of the HSA-Br-NPs via intravitreal route showed significantly higher density RGCs compared to control (sham) group in optic nerve crush (ONC) rat models. Furthermore, they did not detect any brimonidine in retinas after treatment with HSA-NPs which facilitated the improved the survival of RGCs and reduced the deposition of amyloid-β in RGC layer, which showed the inherent therapeutic potential of the nanocarrier materials. Vallejo and his colleagues developed a polypeptide-based controlled nanodrug delivery system of acetazolamide via encapsulation into elastin-like recombinamers (ELRs) by supercritical antisolvent method for glaucoma treatment [99]. The transcorneal permeation studies show a higher apparent permeation coefficient when compared with conventional drug solution, emphasizing the role of ELRs as a potent adsorption promoter for antiglaucoma drug. This innovative use of ELRs for drug permeation demonstrated its potential for improving drug delivery dynamics.

### 6.10. Nanocrystals

Nanocrystals (NCs) is a crystalline solid nanoparticle with an average particle size of less than 1000 nm and entirely comprises of active drug itself. The large surface area of NCs can facilitate enhanced bioavailability without any carrier, such as other nanotherapeutic agents. Furthermore, NCs exhibited rapid early dissolution in first hour, demonstrating improved dissolution and bioavailability [233]. For example, brinzolamide (BRZ) NCs of exhibited higher IOP-lowering efficiency (75 %) compared to marketed eye drops (49 %) [234]. In another study, cellulose NCs and triblockpoloxamer copolymer-based nanocomposites of pilocarpine hydrochloride displayed a sustained and extended drug release profile and fewer toxicity compared to topical *in vitro* gel formulation [235]. Trimethyl lock (TMLo) BRZ prodrug NCs showed comparable therapeutic efficacy to commercial BRZ at low (1/5th) of its molar concentration with negligible toxic effects to cornea of normotensive rats [236].

### 6.11. Polymeric nanofibers

Polymeric NFs are gaining considerable interest as soft materials in ocular field and can readily adhere to the surfaces of the cornea and sclera and cling there for a long time, serving as sustained drug release nanoplatforms [237]. Therefore, compared to liquid or semisolid ocular formulations, electrospun NFs insert might be able to more effectively overcome the precorneal barriers that prevent ocular absorption following topical application [16]. Using NFs insert has led to the observation of longer and higher drug levels in the aqueous humor as well as an increased precorneal residence time [238]. Additionally, NFs provide a stable transmembrane drug gradient that helps in the diffusion of both lipophilic and hydrophilic drug molecule across the ocular structures.

Furthermore, NFs can greatly enhance a system's adhesion to ocular mucins because of their large surface area, distinct surface topology, and porosity. This has already attracted a lot of attention in the pharmaceutical sciences because it can enhance dosage residence time, therapeutic efficacy, and delivery through a variety of administration routes [239]. In addition, NFs insert could be sliced into any form and can easily adapted to the surface of the cornea. The cul-desac volume (about 30 μL) is one of the major obstacles for eye drops that could be easily overawed by using NFs insert.

NFs insert releases the cargo drug at the desired site by three mechanisms, (i) desorption; release of the cargo drug from NFs surface, (ii) diffusion; drug releases from the interior of NFs, (iii) erosion; drug release facilitated by the degradation of polymeric matrix. The factors controlling the drug release are associated with the properties of both NFs as well as the polymers use in fabrication of NFs [240]. For instance, the initial rapid drug release termed as a burst release, often observed in polymeric NFs and corresponds to the fraction of payloads weakly conjugated or adsorbed on the surface of polymeric NFs, rather than entrapped in polymeric NFs. Furthermore, NFs mat can be easily applied to the target site very closely when cut into smaller patches or sheets like therapeutic contact lenses. After adhesion, NFs facilitated the penetration of air and nutrients to eye surface as NFs not cover the entire conjunctive as well as exhibited permeable surface. NFs with mucoadhesive properties actively adhered to the surface of cornea.

For instance, Cegielska et al., fabricated mucoadhesive brinzolamide (BRZ) -loaded NFs as alternative to eye drops for glaucoma treatment [86]. The fabricated NFs exhibited enhanced drug entrapment capacity, from which the cargo drug releases in a controlled and continuous manner. The NFs mat was readily sited on cornea, to eradicate the loss of cargo drug and deliver the therapeutic concentration of drug via different routes. The mucoadhesive NFs offers an inimitable possibility of extending the delivery of cargo drug mainly through cornea after adherence, while not interfering with the disturbed moistness of the glaucomatous eyes. Furthermore, NFs-based, partially degradable glaucoma drainage implant (Nano GDI) significantly prohibited hypotony, and providing a limited aqueous outflow during acute post-surgical phase due degradable core compared to marketed glaucoma drainage implant (Fig. 8) [241]. The imparting of NFs architecture to GDIs to emulate healthy extracellular matrix that would support the fibroblast quiescence to prevent the fibrotic processes which causes failure of marketed glaucoma drainage implants.

In addition to above mentioned advantages of various nanocarriers system in the designing of nanomedicine for glaucoma treatment, nanomedicine also faces some challenges in the treatment of glaucoma. For example, the achieving of therapeutic drug concentration at the target site within the eye is a challenging task as nanomedicines must overcome various biological barriers such as the conjunctiva, cornea,

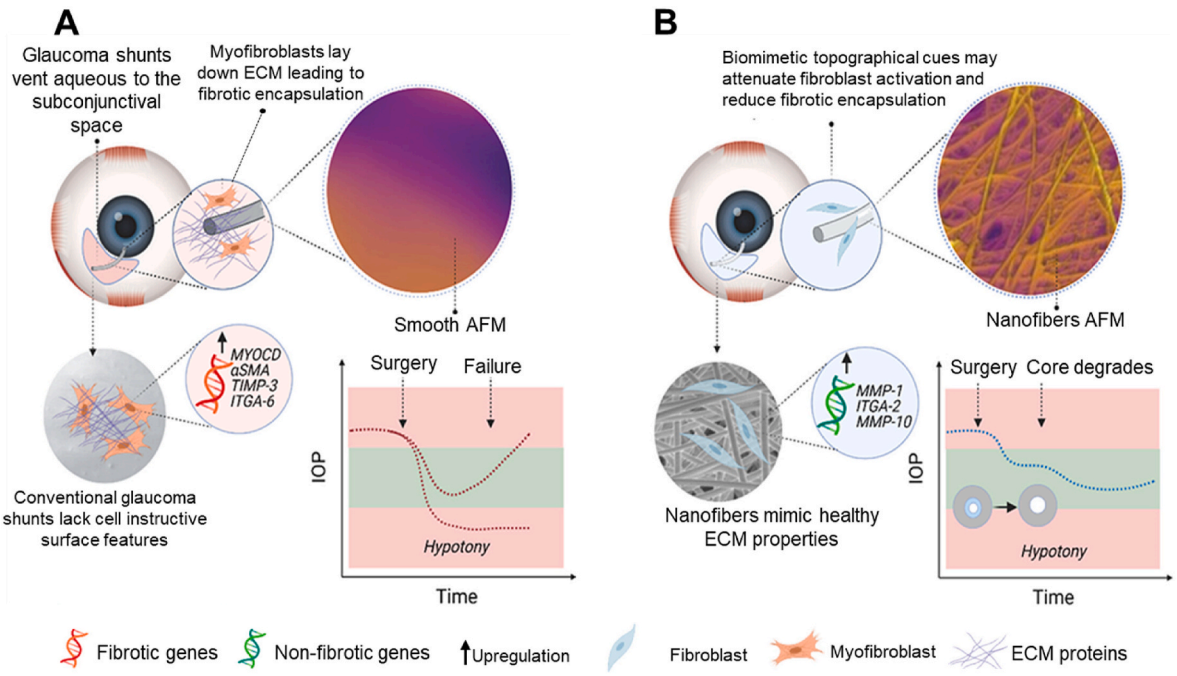


**Fig. 8.** Preventing hypotony and reduce aqueous outflow during acute post-operative phase using (A) Conventional GDI with a smooth surface. (B) NFs-based GDI with healthy ECM. Reproduced from Ref. [241] with permission from Jhon Wiley and Sons.

and blood-aqueous barrier inside eye, to reach the target tissues where therapeutic concentration are desirable. Ensuring the suitable concentration of the drug molecule reaches the target tissues while minimizing systemic exposure is crucial for successful treatment of glaucoma [242].

Secondly, the limited bioavailability of drugs molecule delivered to the target tissue via nanocarrier system. The smaller size nanoparticles readily cleared from the eye leading to reduce therapeutic action. Furthermore, the aggregation and engulfing of nanoparticles by immune cells can further compromise the bioavailability and efficacy of nanomedicine in glaucoma treatment.

Besides, the potential toxicity and biocompatibility of nanomedicines must be carefully addressed to confirm the patient safety. Nanomedicine may cause inflammation in the eye or activate the immune responses, leading to the treatment failure and patient discomfort [2].

## 7. Challenges in clinical translation of nanomedicine

The translation of nanomedicine from the laboratory to clinic is a complex and challenging process, primarily due to several key obstacles related to nanotherapeutic design and development. First, quality control (QC) tests for physicochemical characterization and large-scale production of nanotherapeutics in accordance with Good Manufacturing Practice (GMP) standards are the main barriers in the translation of nanomedicine into clinic. The fundamental components of the product development process, from pre-formulation (lab-scale) to commercialization (production scale), are shown in Fig. 9.

Secondly, in terms of safety, efficacy, stability, and patient acceptability, the marketed product should follow acceptable criteria. The formulation process should follow established guidelines and be repeatable. The treatment efficacy of the nanomedicine entering to clinic be superior or even equal to that of traditional hypotensive eye drops with minimal toxic effect [3].

Thirdly, lacking of satisfactory knowledge and understanding about the intraocular bio-performance of nanopharmaceutical leads to poor clinical translation. Disparate to extraocular or periocular nanomedicine, it's hard to remove the intraocular nanomedicine once administrated into the eyes without using any non-invasive technique.

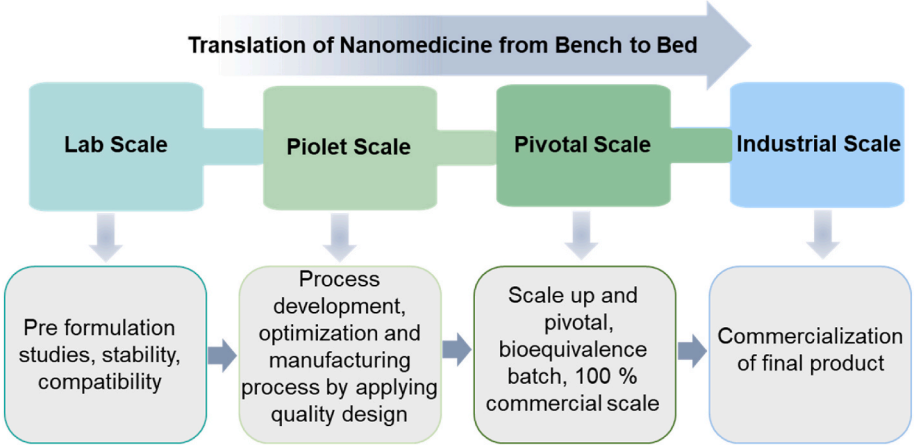


**Fig. 9.** The fundamental components of the product development process, from pre-formulation (lab-scale) to commercialization (production scale).

Researchers might pay special attention to pharmacological responses and biological effect of the constructing materials of nanomedicine before intraocular administration. Studies typically concentrate on the broad physicochemical characteristics of nanosystems, such as particle size, shape, and surface charge. Nevertheless, there hasn't been much investigated on how diverse intraocular environments, like intraocular surgery history, recurrent implantation and vitreous liquefaction in old-aged people eyes might affect the distinct properties of nanomedicine. For example, the movement and clearance of particles after administration in aphakic and vitrectomized eyes [2].

Fourth, the findings from animal model studies might not translate to similar outcomes in human eye, as the anatomy of model eyes significantly differ from human eyes [62]. Rabbits and rats are the most frequently employed in glaucoma models in preclinical research, however neither has a macula in eye. Rats' eyes are considerably smaller than human eyes, measuring around 6 mm in diameter, but their corneal surfaces and lenses are proportionately larger. Although the eye sizes of larger animal models—like rabbits, dogs and pigs are closer to human eyes, this allows for the investigation of surgical methods for the administration of nanomedicine. However, the use of large animals is constrained by the high expense of facilities and maintenance, as well as the remarkable anatomical and physiological differences. The corneas of rabbits are thin which exhibiting less blinking and tearing capacity. Additionally, as they do not have PGA receptors, care should be taken when interpreting the findings of PGA-related research conducted on rabbit models. Despite the fact that non-human primates are the closest anatomically and physiologically to humans, their use is limited by ridiculously high prices and ethical concerns. So, it is necessary to conduct advanced and additional studies on the *in vivo* fate of the nanomedicine in real human eyes across the course of its lifespan, from initial implantation to total biodegradation and retreatment [243].

Fifth, the real-time clinical translation of nanomedicines involved industrial production on large scale, batch-to-batch stability, validation, re-producibility and controllability of physical and both chemical properties. Further, the clinical translation always required an optimized nanoformulation with a developed strategy, so it may be very difficult to produce nanomedicine in reproducible manner when the manufacturing processes is complicated. So, prior to accessing the real-time clinical application, adequate repeatability and large-scale production with low batch-to-batch differences or variation must be addressed [244]. In addition, nanomedicine manufacturing is frequently a multi-step process that involves several different components, and it can be costly and time-consuming [62]. The problem of cost-effectively maintaining repeatability through a robust process can be overcome by multidisciplinary approaches.

Lastly, the invasive nature of intraocular nanomedicine administration carries a higher risk of serious side effects such entophthalmia or retinal detachment. Even with the current standards for intracameral and intravitreal injection, standard operational procedures (SOPs) and procedural recommendations for each type of nanomedicine need to be defined and should be simple to follow in clinical practice easily [2]. According to Kompella et al., the development of intravitreal injection revolutionized the field of ophthalmology due to its established SOPs and the novel biocompatible injectors design. So, this point might be applied to the translation of nanomedicine as all of these recommendations and technologically advanced tools increase therapy acceptance and overall patient safety. In addition, adequate patient adherence and comfort should be considered while designing nanodrug delivery system for ocular delivery [3].

## 8. Future directions

### 8.1. Personalized combinatorial nanomedicine

Considering glaucoma as a multifactorial neurodegeneration disease of RGCs, the combination of therapeutic agents targeting multiple pathophysiological processes in glaucomatous disease might be more effective than monotherapy [95,245]. The simultaneous delivery of two or more therapeutic agents with distinct physicochemical properties is challenging with conventional topical antiglaucoma eye drops; however, it is possible with nanocarrier systems to deliver multiple therapeutic moieties simultaneously. For example, Chan and colleagues constructed a thermosensitive PLGAPEG-PLGA copolymer to transport hydrophilic and hydrophobic molecules (coumarin 6 and rhodamine B) concurrently. One sub-conjunctival injection of prepared nanoplatform could result in a high drug concentration for up to four weeks [246]. In future, personalized combinatorial therapy customized to individual patient's physiological profile based on nanodrug carriers might be a routine choice of glaucoma treatment.

### 8.2. Hybrid nanodrug delivery system (nanoparticles-in-nanofibers)

Nanoparticles-in-nanofibers (NPs-in-NFs) system intricate the development of a hybrid nanosystem by entrapping or embedding NPs into electrospun NFs. A hybrid nanodrug delivery system minimizes the drawbacks of each component while maintaining the advantages of the individual components when compared to a single-originated nanosystem. Furthermore, the overall surface area for pharmacological agent attraction is increased by the entrapped NPs. For example, when high biocompatibility polymers are combined with relatively poor biocompatibility NPs, the exterior polymer matrixes may shield the drug cargo and embedding NPs in live tissues, improving the drug release behavior and lowering biotoxicity [247]. For example, Khalil et al., developed mucoadhesive biodegradable NPs-in-NFs matrix with multilayers act as an advanced and convenient ocular DDS. The incorporation of NPs into electrospun NFs exhibited several advantages such as increased ocular residence, prolonged conjunctival contact time, precise dose delivery, sustained and continuous drug release rate, prolonged drug activity, reduced dose administration frequency, improved bioavailability, low risk of incidence of systemic and visual side effects.

### 8.3. Smart nanomedicine

The word "smart" describes nanomedicine's capacity to deliver and regulated the release of cargo drug in response to exogenous or endogenous stimuli at the precise time and target site. Exogenous stimuli, such as lights, temperature gradients, ultrasounds, electric fields and magnetic fields or endogenous stimuli, such as an enzymatic activity and pH changes, can be used [248]. Smart stimuli-responsive nanodrug delivery systems can deliver the therapeutic moiety to specific site specific in a precise and controllable fashion with negligible toxic or side effects, which still remains challenging task for regular nanomedicine. In addition, controlled and sequential release of cargo drug with multi-stimuli responsiveness might be attained when integrating different stimuli responsive integrant with hybrid nanosystem such as NPs-in-NFs system. Rong et al., designed a glaucomatous microenvironment-sensitive drug carrier polymer containing thioketal bonds and 1,4-dithiane unit [96]. This polymer was employed to encapsulate necrostatin-1, well-known necroptosis inhibitor into nanoparticles which readily release the cargo drug upon interaction with ROS in glaucomatous microenvironment.

## 9. Concluding remarks

Globally, glaucoma is a serious condition that can cause blindness to people of all ages. The main barriers to using topical eye drops for glaucoma treatment are patient non-adherence and the drugs' poor bioavailability, particularly for a chronic condition like glaucoma that needs daily, lifelong treatment with repeated doses. Nanomedicine based therapeutic strategies with lot of potentials are promising for glaucoma treatment as they are effective in providing prolonged release, target delivery, higher bioavailability, decreased side effects, improved

patient compliance and increased treatment success. Despite promising potential and prospects of nanomedicine, there are still issues that need to be resolved. These include reliable and affordable scale-up production, safety and efficacy studies conducted at various stages of the system's lifecycle in various intraocular environments prior to official approval and commercialization. The aforementioned questions still need to be thoroughly investigated in order to successfully complete the bench-to-bedside translation of nanomedicine. With substantial advancement and multidisciplinary research discoveries, both patients and clinicians are looking forward to more advance and potential therapeutic approaches might be available clinic for glaucoma treatment near future.

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## CRediT authorship contribution statement

**Haroon Iqbal:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Conceptualization. **Anam Razzaq:** Writing – original draft, Formal analysis, Data curation. **Dengming Zhou:** Formal analysis, Visualization. **Jiangtao Lou:** Visualization, Validation. **Run Xiao:** Writing – review & editing, Resources. **Fu Lin:** Writing – review & editing, Visualization, Supervision. **Yuanbo Liang:** Writing – review & editing, Visualization, Supervision, Resources, Project administration, Funding acquisition.

## Declaration of competing interest

The authors report there are no competing interests to declare.

## Data availability

Data will be made available on request.

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