



Gold Nanoparticle Shape Design for Ophthalmic Imaging and Therapy

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Abstract

Ocular drug delivery remains challenging due to the eye's complex anatomical and physiological barriers, which significantly limit effective drug penetration and retention. Among the various nanocarrier systems developed, gold nanoparticles have shown considerable potential for overcoming ocular barriers and facilitating drug delivery across the cornea and conjunctival epithelia. Gold nanoparticles have been extensively investigated for the diagnosis and treatment of ocular diseases, including glaucoma, diabetic retinopathy, and age-related macular degeneration. The properties and functionalities of gold nanoparticles are strongly dependent on particle size and shape, both of which can be precisely controlled through various synthesis approaches. Owing to their reported biocompatibility, relatively low toxicity, tunable optical properties, and adjustable surface plasmon resonance, the use of gold nanoparticles in ophthalmology has increased significantly in recent years. The current review presents the therapeutic and diagnostic applications of gold nanoparticles in ocular systems from a morphology-oriented perspective. It highlights their impact on ocular delivery efficiency and imaging performance while also considering key parameters such as particle size, surface coating, and functionalization.

Keywords:

gold nanoparticles; ophthalmology; morphology; nanospheres; nanorods; nanostars; optical coherence tomography

1. Introduction

According to the World Health Organization (WHO), more than 2 billion people were affected by vision impairment in 2019 [1,2]. Drug delivery to the eye remains challenging due to its unique anatomical and physiological barriers. Although these barriers protect the eye against toxins and microorganisms and contribute to ocular immune privilege, they also pose significant challenges for the effective management of eye diseases. Several ocular drug delivery routes have been investigated for the administration of various therapeutics, including topical, subconjunctival, subretinal, and intravitreal (Figure 1) [3]. These approaches differ in terms of the targeted ocular tis-

sues, administration volume, degree of invasiveness, and associated advantages and limitations. Various periocular delivery routes have been explored as less invasive alternatives to intravitreal injections. However, conventional ocular dosage forms, such as eye drops and ointments, exhibit low bioavailability and limited therapeutic efficacy due to the eye's inherent protective mechanisms, including the blinking reflex, nasolacrimal drainage, short precorneal residence time, and restricted corneal permeability [4]. For example, topical administration (e.g., eye drops) primarily targets the anterior segment of the eye, including the cornea and conjunctiva. However, it is

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limited by low bioavailability (typically less than 5%) due to anatomical barriers and rapid tear drainage. In addition, only small volumes (approximately 30–50 μL per drop) can be administered, often requiring frequent dosing to maintain therapeutic levels. Despite these limitations, this route remains widely used due to its non-invasive nature and ease of self-administration [5]. Intravitreal injections deliver drugs directly into the vitreous cavity near the retina, allowing high concentrations at the posterior segment, but require small injection volumes (0.05–0.1 mL). Intravitreal injections are invasive procedures associated with risks such as ocular infection and retinal detachment, and often require frequent clinical visits for repeated administration [6]. Periocular routes (e.g., subconjunctival and sub-tenon) can target both anterior and posterior segments by delivering drugs into tissues surround-

ing the eye. These approaches permit larger administration volumes than topical delivery and may bypass certain ocular barriers; however, they generally remain less direct than intravitreal injection for posterior segment delivery. However, they remain invasive and may be associated with complications such as patient discomfort and hemorrhage. Systemic administration, either oral or intravenous, is generally less effective for targeted ocular drug delivery because of limited ocular penetration and low drug accumulation within ocular tissues. Nevertheless, it may be appropriate for the treatment of systemic diseases with ocular manifestations [7]. Consequently, repeated administration of highly concentrated formulations is often required to achieve the desired therapeutic effect, which can adversely affect patient compliance.

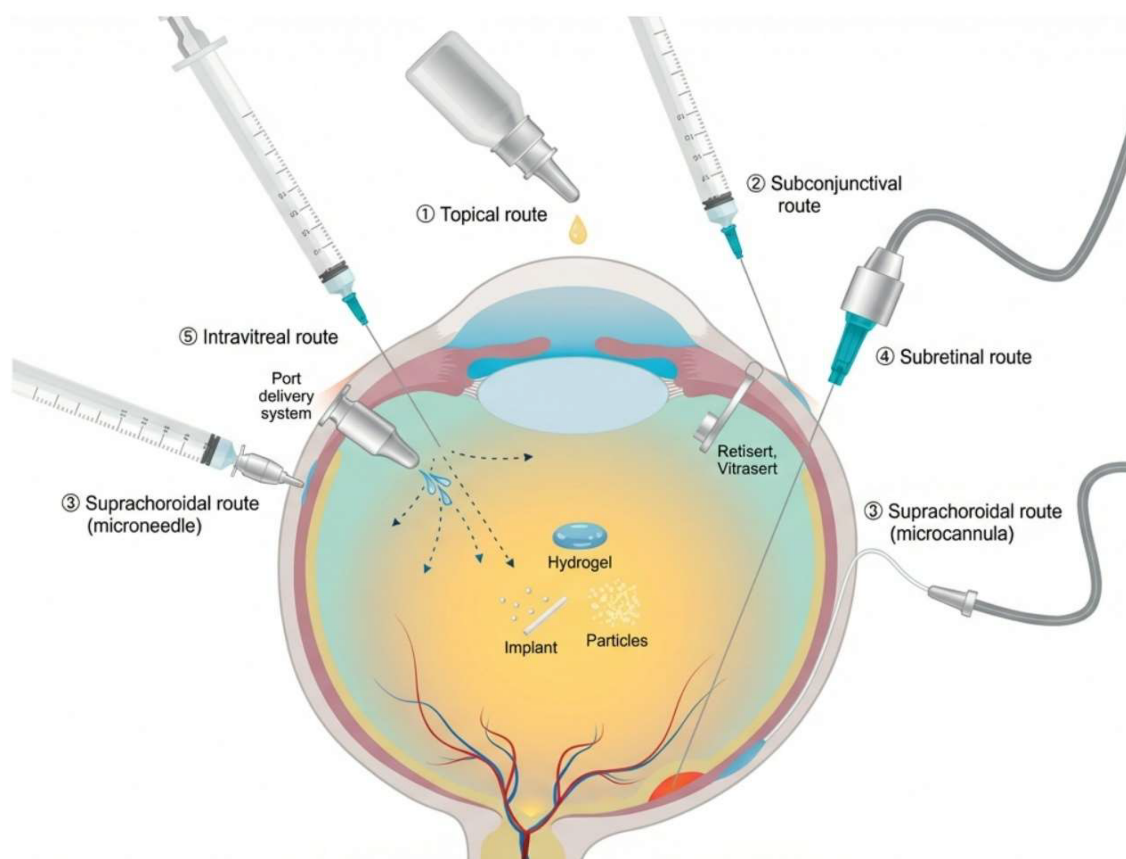


Figure 1: Examples of the commonly exploited administration routes for ocular drug delivery: (1) topical, (2) subconjunctival, (3) suprachoroidal, (4) subretinal, and (5) intravitreal injection and port delivery system. Reproduced from [3] (under the license of CC BY 4.0).

Several studies have highlighted the barriers and limitations associated with ocular drug delivery and have examined the influence of drug physicochemical properties on ocular bioavailability. Invasive approaches, such as

intravitreal injections, enable direct drug delivery to the posterior segment and achieve high intraocular drug concentrations. However, these procedures are associated with risks such as infection and optic nerve damage and

may reduce patient compliance because of their invasive and repetitive nature [8]. In contrast, non-invasive approaches such as topical eye drops are widely preferred due to their safety, ease of administration, and high patient compliance. However, they are constrained by multiple ocular barriers, including the corneal epithelium, conjunctiva, sclera, tear film, and dynamic clearance mechanisms, which collectively result in extremely low bioavailability and limited drug penetration to the posterior segment [9]. These static and dynamic barriers, including tear turnover, nasolacrimal drainage, and blood-ocular barriers, limit both the rate and extent of drug delivery, thereby necessitating frequent dosing and resulting in suboptimal therapeutic outcomes and reduced patient compliance [10]. Therefore, overcoming these route-specific ocular barriers remains a central challenge in the development of effective ocular drug delivery systems [11]. Nanotechnology-based drug delivery systems may improve ocular residence time, drug penetration, controlled release, and therapeutic efficacy compared with conventional formulations.

Nanocarriers of various types, shapes, and morphologies have been exploited for diverse biomedical applications, including ocular delivery [12–16]. Nanoparticle morphology plays a critical role in determining therapeutic efficacy by influencing cellular binding and uptake, drug release kinetics, biodistribution, and intracellular residence time [17–19]. (However, because of the heterogeneous nature of organs, tissues, and cells within the body, a “one-size-fits-all” approach to nanoparticle design is not applicable [20,21]. Nanoparticle-based formulations, such as polymeric nanoparticles, liposomes, and niosomes, have been developed for the treatment of various ocular diseases, including glaucoma, age-related macular degeneration, autoimmune uveitis, and corneal and choroidal neovascularization [4,22]. Improved therapeutic outcomes can be achieved by increasing residence time in the precorneal region, improving drug interactions with the ocular surface and target tissues, and enabling sustained and controlled drug release in corneal tissues [3,13,23–32]. Extensive preclinical and clinical research has been conducted to develop nanoscale drug delivery systems for the treatment of a wide range of ocular diseases [33–35].

Various nanocarrier systems have demonstrated the ability to overcome ocular barriers and facilitate drug delivery across the corneal and conjunctival epithelia [36–39]. Among these nanosystems, gold nanoparticles of var-

ious morphologies have been described as potential delivery systems for managing ocular diseases, as well as for diagnostic and photothermal applications. Considering the substantial influence of nanoparticle morphology on therapeutic and diagnostic performance in ocular applications, this review examines how gold nanoparticle morphology affects ocular delivery and treatment outcomes. In addition, it discusses the roles of key physicochemical parameters, including particle size, surface coating, and surface functionalization, in modulating their efficacy.

2. Gold Nanoparticles and the Control over Their Shape

Significant advances in the controlled synthesis of gold nanomaterials have enabled precise tuning of their size, shape, and surface chemistry, facilitating a wide range of applications, including optical, biological, and electronic technologies [40]. Several approaches (i.e., physical, chemical, biological, and electrochemical) have been described in the literature for synthesizing gold nanoparticles of various sizes and morphologies (Figures 2 and 3). Chemical methods, such as the Turkevich and seed-mediated approaches, are commonly employed for the synthesis of gold nanoparticles. These methods typically involve two main steps: reduction of gold precursors and subsequent stabilization of the formed nanoparticles. In the Turkevich method, gold nanoparticles are synthesized by treating a chloroauric acid solution with sodium citrate, which serves as both a reducing agent and a stabilizer, preventing the particles from aggregating. The seed growth method enables the control of particle size and geometry of gold nanoparticles by adjusting the concentrations of seeds, structure-guiding agents, and reducing agents. Physical synthesis approaches employ radiation-based techniques, such as gamma irradiation, laser ablation, and microwave-assisted methods, to produce highly pure, homogeneous gold nanoparticles with sizes typically ≤ 40 nm [41]. Biological methods provide a sustainable, environmentally friendly, and cleaner alternative to conventional chemical synthesis approaches. These approaches utilize biological systems, including bacteria, fungi, and plant extracts, to synthesize gold nanoparticles while offering enhanced control over their morphology. Several reviews provide detailed procedures for the synthesis of gold nanoparticles and the tuning of their morphology [40,42,43].

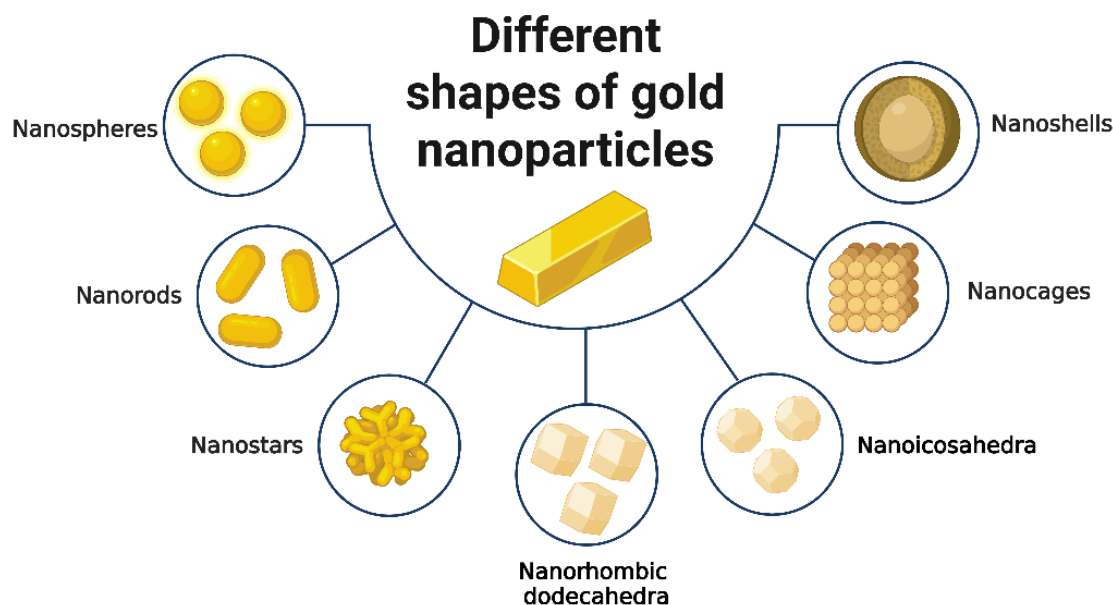


Figure 2: Different shapes of gold nanoparticles. Created by BioRender.com.

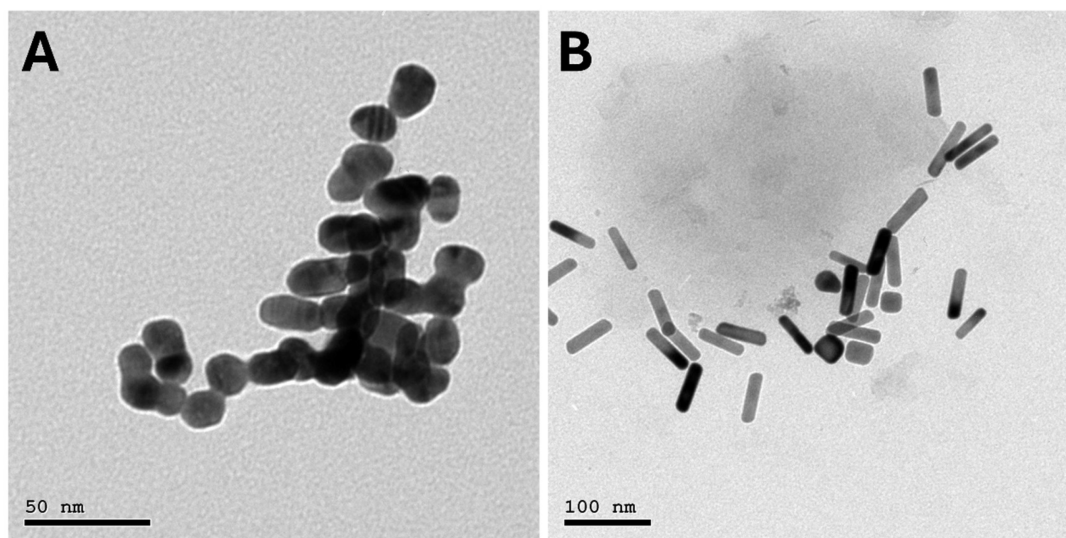


Figure 3: TEM images of gold nanoparticles: (A) spherical nanoparticles and (B) rod-shaped nanoparticles.

3. Gold Nanoparticles of Various Morphologies for Ocular Applications

The optical properties of gold nanomaterials are significantly influenced by their size and shape (spherical, nanorods, nanostars, etc.). Their surface plasmon resonance, arising from collective oscillations of surface electrons, is further modulated by the surrounding medium and the particle's geometric cross-section. Hence, accu-

rate adjustment of these features enables exceptional multifunctionality in molecular diagnostics and biosensing. The tunable physicochemical properties of gold nanostructures, together with the ability to modify their structural dimensions through various fabrication techniques, have made these materials promising candidates for applications in colorimetric analysis, biosensing, photothermal transduction, and biomedical imaging [40].

Gold nanoparticles have been exploited for diagnostic purposes and for the treatment of ocular diseases. The

development of gold nanoparticles with diverse morphologies (Figure 2) has greatly influenced their imaging and therapeutic applications [44]. For example, tuning the shape of gold nanoparticles enables precise modulation of their optical properties, which can enhance penetration into deeper ocular tissues and thereby improve diagnostic and theranostic performance. Spherical gold nanoparticles are easy to synthesize, highly biocompatible, and stable in suspension, which helps prevent agglomeration and ensures uniform cellular distribution, but their optical absorption is limited to 500–580 nm, restricting deep tissue imaging and therapy unless aggregated to shift their plasmon resonance to the NIR region [45]. Their spherical morphology also enhances interactions with cellular membranes, promoting efficient cellular uptake and more

uniform intracellular distribution, thereby improving therapeutic efficacy. In contrast, non-spherical gold nanoparticles, such as nanorods and nanostars, offer tunable optical properties with plasmon resonance in the NIR region (up to 1000 nm for rods and 700–900 nm for stars), enabling deeper tissue penetration and stronger imaging contrast in ophthalmic imaging modalities like photoacoustic imaging and optical coherence tomography (OCT) [46]. Non-spherical morphologies, particularly nanostars, generate stronger localized electric fields and larger scattering cross-sections, leading to enhanced signal amplification for imaging and therapeutic applications (Figure 4) [47]. The following sections review the application of spherical and nonspherical gold nanoparticles in various ocular applications (Table 1).

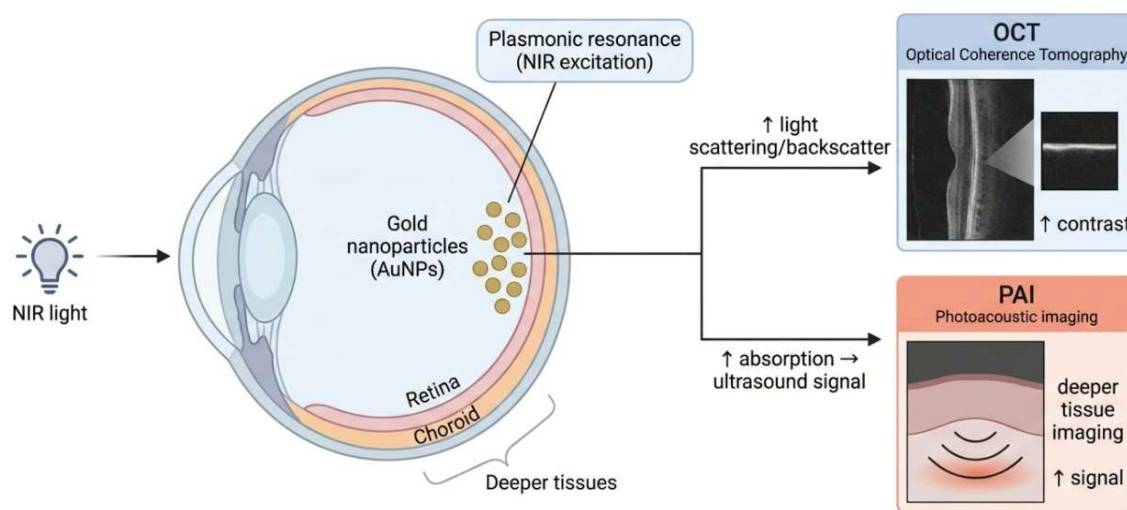


Figure 4: Schematic illustrating the use of gold nanoparticles in ocular imaging. Created by BioRender.com.

3.1. Spherical Gold Nanoparticles: Size and Surface Considerations

Spherical gold nanoparticles have been widely reported in the literature for the management of ocular diseases. In addition, surface modification and functionalization of gold nanoparticles can enhance their mobility and permeability across ocular barriers (Figure 5). For example, Apaolaza and coworkers developed gold nanoparticles as a promising delivery system for addressing ocular neovascularization and related disorders [48]. In their study, gold nanoparticles were coated with low-molecular-weight hyaluronan to enhance nanoparticle permeability and enable targeting of CD44 receptors, which are expressed in ocular tissues and exhibit affinity for hyaluronic acid. The nanoparticles were synthesized in two distinct

sizes (21.88 and 50.26 nm), and coating resulted in a substantial increase in hydrodynamic diameter, with the functionalized nanoparticles reaching 53.22 and 90.01 nm, approximately double the size of their uncoated counterparts. During a 4-week in vitro study, coated gold nanoparticles exhibited enhanced stability and increased resistance to protein corona formation. Moreover, despite the increase in particle size following coating, hyaluronic acid functionalization improved diffusion within the vitreous matrix and facilitated penetration into retinal layers, which was not observed with uncoated gold nanoparticles, as confirmed by transmission electron microscopy. Coating gold nanoparticles with hyaluronic acid provides an additional benefit of CD44 targeting, an overexpressed protein in several ocular diseases [48]. The affinity of CD44 receptors for hyaluronic acid facilitates enhanced

cell adhesion and promotes receptor-mediated endocytosis of hyaluronic acid-conjugated drugs or delivery systems. Sonntag and co-workers investigated the optimal size of gold nanoparticles for targeting the trabecular meshwork, a tissue involved in aqueous humor outflow [49], for potential encapsulation and delivery of anti-glaucoma drugs [50]. In their study, spherical nanoparti-

cles of different sizes (i.e., 5, 60, 80, and 120 nm) were examined, either uncoated or coated with hyaluronic acid, for enhancing colloidal stability. Coating with hyaluronic acid resulted in a slight increase in particle size (2–14 nm) while providing superior colloidal stability compared with uncoated nanoparticles.

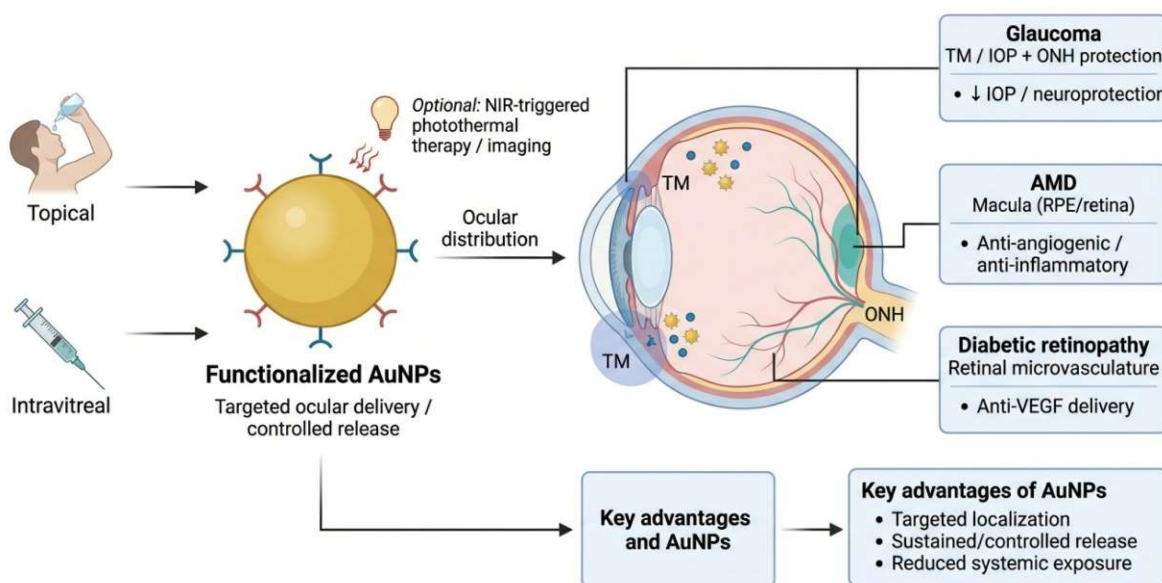


Figure 5: Schematic illustrating the targeted ocular delivery of functionalized gold nanoparticles. Created by BioRender.com.

Ex vivo perfusion studies of porcine eyes were carried out to assess the gold content of each tissue sample of the anterior eye chamber (ciliary body, cornea, iris, lens, and trabecular meshwork) 6 h after injection of the gold nanoparticles. A higher number of 5 nm gold nanoparticles was detected in the trabecular meshwork. However, a greater overall gold content was observed for larger-sized nanoparticles. This was attributed to the higher volume-based accumulation in the trabecular meshwork (i.e., increased overall particle volume in the tissue). Hyaluronic acid-coated gold nanoparticles with larger sizes (60 and 120 nm) demonstrated both extracellular and intracellular distribution within the trabecular meshwork, as confirmed by transmission electron microscopy (Figure 6), with no significant differences observed between the two particle sizes. The study concluded that the developed gold nanoparticles could be formulated as a depot system to overcome the rapid turnover of aqueous humor, enabling sustained drug release into the anterior chamber and subsequent distribution to the trabecular meshwork [50]. In an in vivo mouse model, topical application of hyaluronic acid-coated gold nanoparticles demon-

strated significantly enhanced distribution in the posterior segment of the eye as compared to their uncoated counterparts (Figure 7) [51].

PEGylation of gold nanoparticles (i.e., coating gold nanoparticles with polyethylene glycol (PEG)) can reduce nonspecific protein adsorption, including proteins involved in opsonization, and thereby prolong systemic circulation time [52]. A ranibizumab biosimilar (Mab), a biosimilar of ranibizumab and a vascular endothelial growth factor (VEGF)-specific antibody fragment used as a standard therapy for the management of age-related macular degeneration, has been conjugated to PEGylated gold nanoparticles. The Matrigel-based tube formation assay was used to assess the anti-angiogenic activity of the developed nanoparticles. The in vitro assay demonstrated stronger inhibition of tube formation in human umbilical vein endothelial cells treated with Mab/PEGylated gold nanoparticles than in those treated with PEGylated gold nanoparticles alone; however, both formulations exhibited anti-angiogenic activity [53]. This was attributed to the possible attenuation of the VEGF-A effect due to its binding with gold nanoparticles.

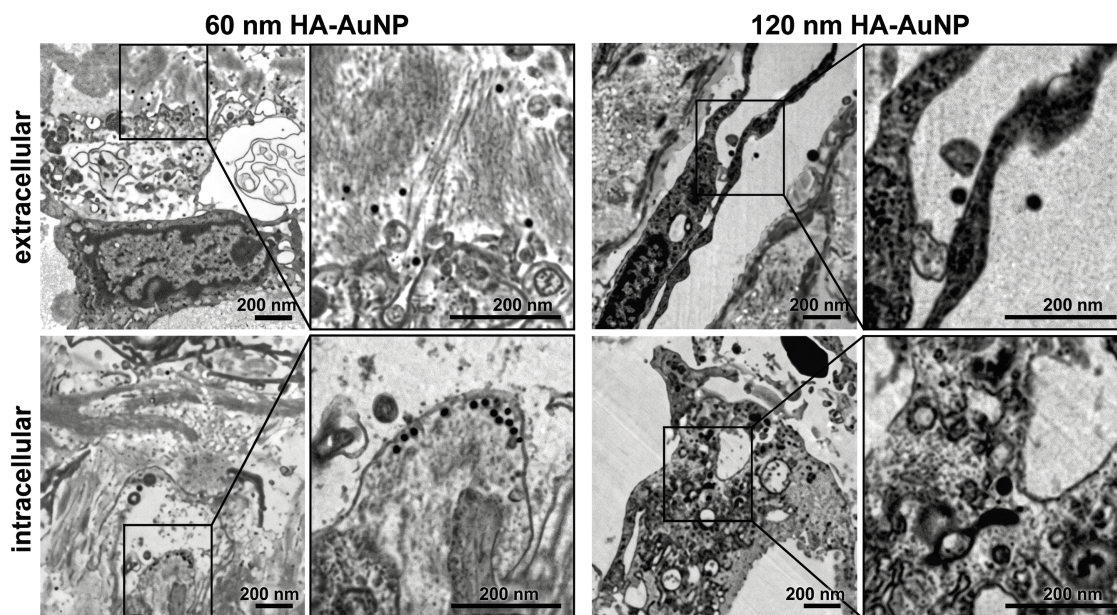


Figure 6: Distribution of gold nanoparticles within the trabecular meshwork after ex vivo perfusion with hyaluronic acid-coated gold nanoparticles (60 and 120 nm). Right-hand images are magnifications of the marked areas of the left-hand images; scale bars = 1 μ m. Reproduced from Ref. [50] (under the license of CC BY 4.0).

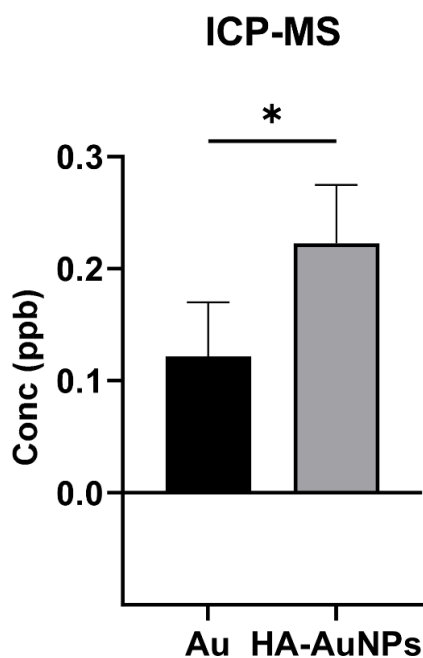


Figure 7: Inductively coupled plasma mass spectrometry analysis of the posterior segment of the eye demonstrates enhanced distribution of coated gold nanoparticles. (* $p < 0.05$). Reproduced from Ref. [51] (under the license of CC BY 4.0).

Therapeutic contact lenses have been utilized as a strategy for ophthalmic drug delivery to overcome the limited bioavailability of traditional eye drops, while minimizing the need for frequent or high-dose adminis-

tration [43,44]. The use of drug-laden contact lenses has demonstrated enhanced ocular bioavailability. These lenses can be fabricated using various techniques, including conventional soaking, molecular imprinting, and ion-ligand gel systems. These techniques aim to enhance drug loading and control drug release while preserving the optical and physicochemical properties of the lens, including transparency, contact angle, and swelling behavior. To enhance drug loading via the soaking method, Maulvi et al. investigated the incorporation of spherical gold nanoparticles either during contact lens fabrication (yielding gold nanoparticle-laden contact lenses) or within the drug-soaking solution. Both approaches demonstrated improved loading and uptake of timolol, an anti-glaucoma drug, into the contact lenses without altering the critical characteristics of the lens (i.e., swelling and optical transparency) [54].

Although in vitro release profiles were not significantly improved in either approach, in vivo studies showed a prolonged reduction in intraocular pressure in the rabbits' eyes treated with gold nanoparticle-laden contact lenses. A higher drug accumulation was observed in the iris-ciliary muscle, which was attributed to the incorporation of gold nanoparticles within the contact lenses, enhancing drug permeability and tissue retention [54]. Similarly, Guo and co-authors demonstrated that gold nanoparticle-laden contact lenses enhanced ketotifen uptake from a drug-soaking solution and improved both in vitro and in vivo performance without altering the in-

trinsic properties of the contact lenses [55]. Spherical gold nanoparticles were incorporated either within the contact lens matrix or into the soaking solution to overcome the limitations of the conventional soaking method, including alterations in the mechanical properties and ion permeability of the contact lenses. The study demonstrated that contact lenses loaded with nanoparticles enhanced drug uptake from the soaking solution compared with both the conventional drug solution and the nanoparticle-containing solution alone. Moreover, lower burst release and sustained drug release for up to 96 h were achieved when gold nanoparticles were incorporated into the contact lens matrix. In vivo studies further demonstrated consistently higher ketotifen concentrations in rabbit tear fluid at all time points compared with both the drug-soaked contact lens and ketotifen eye drop formulations. In contrast, the ketotifen eye drop solution exhibited a rapid initial burst release with limited drug retention, becoming undetectable after 12 h. In comparison, the gold nanoparticle-laden contact lens demonstrated sustained drug retention for up to 72 h. Interestingly, no ocular irritation was reported, and histopathological studies demonstrated normal corneal histopathology during the in vivo study over 72 h. Notably, the gold nanoparticle-laden contact lens exhibited negligible changes in optical transmittance compared with the contact lens prepared using the traditional soaking method, which showed a significant reduction in transmittance [55].

Gold nanoparticles have also been incorporated into other nanosystems, such as liposomes, alongside therapeutic agents to act as contrast enhancers for drug delivery to the posterior segment of the eye. For instance, Salem and co-authors developed flucytosine-capped, gold nanoparticle-loaded liposomes to improve intraocular penetration of the drug and to evaluate its antifungal efficacy following topical ocular administration [56]. The developed formulations demonstrated significant in vitro antifungal activity against *Candida albicans* compared with the free flucytosine and gold nanoparticle solutions. Among the tested nanosystems, formulation F6, comprising flucytosine and gold nanoparticles encapsulated in phosphatidylcholine, cholesterol, span 60, and stearylamine at a molar ratio of 1:1:1:0.15, exhibited the largest mean diameter of the growth inhibition zone. The incorporation of gold nanoparticles with the drug into liposomes enhanced antifungal activity. This effect was attributed to the accumulation of insoluble gold within the fungal cell wall, which disrupted transmembrane energy metabolism and impaired the membrane electron transport chain [57]. Gold nanoparticles may also induce fungal DNA mutations and disrupt fungal enzyme complexes, both of which are essential for the respiratory chain and membrane per-

meability. In vivo CT imaging of rabbit eyes following administration of flucytosine-capped, gold nanoparticle-loaded liposomes demonstrated progressive nanoparticle diffusion over a six-hour period, with the optimal formulation exhibiting the greatest permeation distance within ocular tissues. The optimal formulation demonstrated enhanced relative bioavailability, attributed to the prolonged residence time of the tested formulation, which facilitated increased flucytosine absorption. In vivo studies in rabbits demonstrated the superior antifungal activity of formulation F6 compared with flucytosine solution, as evidenced by the healing and clearance of *Candida* keratitis in infected eyes.

3.2. Nonspherical Gold Nanoparticles: Size and Surface Considerations

Nonspherical gold nanoparticles have been exploited for various applications (e.g., photothermal therapy, drug delivery, bio-imaging, and bio-sensing). They are increasingly being explored for ocular applications due to their unique physicochemical properties, including their strong optical response in the near-infrared window. For example, gold nanorods have been used as exogenous chromophores to enable near-infrared laser welding of ocular connective tissues [58]. Gold nanorods have been used as a self-therapeutic agent to prevent tumor growth; however, different mechanisms of action to limit angiogenesis have been reported [59,60]. Uncoated gold nanoparticles have demonstrated anti-angiogenic activity, as evidenced by inhibition of VEGF-induced endothelial cell proliferation in vitro and suppression of VEGF-induced angiogenesis in vivo. The suppression of angiogenesis was attributed to the binding affinity of gold nanoparticles to VEGF [61,62]. In this context, Song and co-workers synthesized gold nanodisks to evaluate their inhibitory effect on retinal neovascularization [63]. The authors fabricated gold nanodisks of various diameters and selected the 160 nm-sized nanodisks, which exhibited strong optical coherence tomography (OCT) signals in a dose-dependent manner following intravitreal injection into mouse eyes. In an in vitro wound healing assay, the nanodisks suppressed VEGF-induced migration of human retinal microvascular endothelial cells without inducing cytotoxicity after 48 h of incubation at the highest tested concentrations. In an oxygen-induced retinopathy mouse model, intravitreal administration of the gold nanodisks (1 and 3 pM) reduced neovascularization in a dose-dependent manner without inducing toxicity, as confirmed by histological analysis showing preserved tissue integrity and absence of inflammation. The gold nanodisks were cleared entirely within 14 days, with no detectable accumulation on the inner lim-

iting membranes [63]. In another study, PEGylated gold nanorods were shown to disrupt retinal angiogenesis and tumor progression by selectively interfering with endothelial cell cytokinesis, leading to the formation of binucleated cells that are unable to proliferate [59]. The study revealed that PEGylated gold nanorods specifically targeted endothelial cell cytokinesis without inducing DNA damage, apoptosis, or autophagy. The PEGylated gold nanorods were biocompatible and specifically disrupted the assembly of actin filaments in the contractile ring site.

Gold nanorods have also been utilized as contrast agents for photothermal optical coherence tomography (PTOCT) due to their high absorption coefficient at the irradiation wavelength used for photothermal excitation in PTOCT [64,65]. In a laser-induced choroidal neovascularization (LCNV) animal model, Lapierre-Landry and co-workers investigated the use of gold nanorods as contrast agents and demonstrated that photothermal optical coherence tomography (PTOCT) could effectively detect their presence within lesions [66]. Building on the observation that multiple antibody-targetable surface ligands are upregulated in laser-induced lesions, including ICAM2, a constitutively expressed marker on vascular endothelial cells, the same research group demonstrated that photothermal optical coherence tomography (PTOCT) imaging of both untargeted and ICAM2-targeted gold nanorods produced an enhanced lesion-associated photothermal signal during imaging. The study demonstrated the detection of anti-VEGF-induced changes in the mouse retina in a laser-induced choroidal neovascularization (LCNV) model, as evidenced by a significant reduction in the accumulation of ICAM2-targeted gold nanorods following anti-VEGF treatment [67]. This molecular information could contribute to the early detection and therapeutic intervention in patients with sight-threatening diseases.

Multimodal optical coherence tomography (OCT) and photoacoustic microscopy (PAM) enable early diagnosis of several ocular conditions, including wet age-related macular degeneration, which is characterized by the development of choroidal neovascularization (CNV), a network of structurally disorganized, leaky blood vessels. To enhance the sensitivity of molecular imaging, the morphology of conventional spherical gold nanoparticles can be engineered into alternative structures, such as nanostars, which induce a red shift in plasmonic absorption into the near-infrared (NIR) region, thereby improving imaging depth and contrast [68]. Nguyen and coauthors utilized gold nanostars as molecular contrast agents to visualize neovascularization through multimodal photoacoustic microscopy (PAM) and optical coherence tomography (OCT) imaging [69]. In this study, gold nanos-

tars functionalized with the arginine-glycine-aspartic acid (RGD) peptide, which binds to the integrin $\alpha v \beta 3$ receptor overexpressed in CNV, demonstrated high photostability and no observable toxicity at the tested concentration (5 mg/mL) [69]. Owing to the red-shifted plasmonic absorption, gold nanostars significantly enhanced imaging signals, with up to a 17-fold increase in photoacoustic microscopy (PAM) and a 167% improvement in optical coherence tomography (OCT), enabling clear delineation of choroidal neovascularization (CNV) margins from surrounding native tissues in rabbits (Figure 8). Enhanced OCT contrast can be achieved by tuning the size and morphology of gold nanostars, including variation in the number of branches and their aspect ratios, as well as increasing the core size of the nanostars prior to seed-mediated growth [70]. As with gold nanostars, intravenous administration of gold nanorods functionalized with the RGD ligand into a CNV rabbit model resulted in a 27.2-fold increase in PAM and 171.4% increase in OCT owing to the strong absorption and scattering properties of the gold nanorods [71].

The use of nonspherical gold nanoparticles effectively overcomes limitations associated with their spherical counterparts. Although spherical gold nanoparticles can enhance photoacoustic and OCT signals, their peak absorption wavelength overlaps with that of hemoglobin, thereby limiting contrast enhancement in biological tissues. Nonspherical morphologies exhibit a shifted plasmonic peak absorption from the visible to the near-infrared region. In this spectral region, intrinsic optical absorption by native chromophores is considerably reduced, thereby enhancing the sensitivity of molecular imaging [1]. Anisotropic gold nanoparticles are more efficient photothermal transducers for plasmonic photothermal therapy (PPTT). Although gold nanobipyramids exhibit excellent photothermal performance, their limited short-term stability arising from tip shortening and loss of sharp features can adversely affect their plasmonic properties for photothermal therapy (PTT) [72]. Accordingly, surface stabilization of gold nanobipyramids using coatings such as citrate was performed, resulting in nanoparticles that exhibited the highest temperature increase (40 °C at 2.0 W cm⁻²) after 15 min of 808 nm near-infrared (NIR) laser irradiation. This substantial temperature increase is critical for effective photothermal therapy (PTT), as it can induce the desired therapeutic effects while minimizing damage to surrounding tissues, as supported by in vitro cytotoxicity studies demonstrating nanoparticle biocompatibility with major corneal cell types, including human corneal endothelial cells, human corneal fibroblasts, and corneal epithelial cells [72].

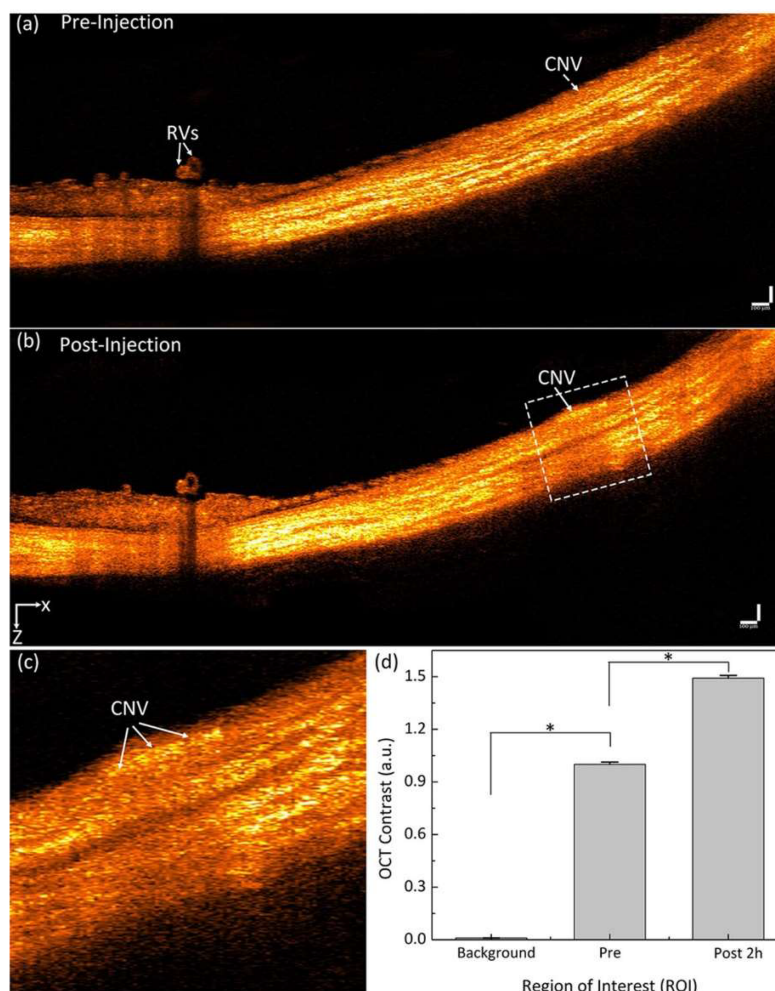


Figure 8: Enhanced in vivo OCT imaging contrast using gold nanostars: (a,b) B-scan OCT images before and two h after intravenous gold nanostars injection. White arrows indicate CNV position. (c) Magnified view of the area outlined in (b). (d) Spectral analysis of OCT intensity within the CNV before and two h after gold nanostars administration. Reproduced with permission from Ref. [69] (© [American Chemical Society]. Permission obtained via Copyright Clearance Center (CCC) RightsLink).

Although several studies have investigated the influence of size, shape, aspect ratio, and surface chemistry on pharmacokinetics, biodistribution, cellular uptake, and therapeutic efficacy in general biomedical applications [73–77], comparative studies evaluating the impact of nanoparticle morphology on ocular drug delivery remain limited. Among the physicochemical properties, the shape and morphology displayed significant effects on cellular binding, uptake, and pharmacological activities [12,18,21,78–82]. To date, only a limited number of studies have directly investigated and compared the influence of gold nanoparticle morphology on ocular therapy. In previous work, spherical and rod-shaped gold nanoparticles loaded with a carbonic anhydrase inhibitor were compared for glaucoma management [12]. Spherical gold nanoparticles demonstrated superior efficacy in reducing intraocular pressure compared with their rod-shaped coun-

terparts in a rabbit glaucoma model. This improved performance was attributed to enhanced ocular retention of spherical drug-loaded nanoparticles within stromal collagen fibers, as confirmed by transmission electron microscopy (TEM) imaging. Eye irritation testing demonstrated excellent ocular tolerance for the drug-loaded gold nanospheres. The rod-shaped counterpart showed signs of irritation in the cornea, conjunctiva, and iris, which may be attributed to residual cationic CTAB, a surfactant commonly used during gold nanorod synthesis to promote axial growth [12,83]. Normal microscopic architecture of the cornea and retina, with no evidence of inflammation or tissue abnormalities, was observed in eyes treated with spherical gold nanoparticles, whereas tissue abnormalities were detected in eyes treated with the rod-shaped counterparts.

Table 1: Gold nanoparticles for ocular applications. TEM: transmission electron microscopy, DLS: dynamic light scattering.

	Composition	Size of Gold Nanoparticles	Remarks	Advantages	References
Spherical gold nanoparticles	Hyaluronan-coated gold nanoparticles	- Uncoated (21.88 ± 0.98 and 50.26 ± 1.78 nm)	- Coated gold nanoparticles demonstrated higher stability and resistance to the formation of protein corona.	Enhanced stability, targeted delivery <i>via</i> CD44 receptor binding, and improved diffusion across ocular barriers	[48]
		- Coated (53.22 ± 3.36 and 90.01 ± 2.58 nm)	- Coating with hyaluronic acid enhanced stability, facilitated diffusion across cell membranes and tissues, and enabled targeting through specific CD44 receptor interaction.		
			- Ex vivo, the ability of coated gold nanoparticles to diffuse through the vitreous humor and their affinity to reach the deeper retinal layers indicate their potential for the treatment of intraocular vascular diseases.		
	Hyaluronic acid-coated gold nanoparticles	15–20 nm	- In an in vivo mouse model, topical application of hyaluronic acid-coated gold nanoparticles demonstrated greater distribution in the posterior eye segment (retinal layers) as compared to uncoated ones.	Non-toxicity, efficient biodistribution, and active site-specific targeting via hyaluronic acid-CD44 affinity	[51]
	Ranibizumab biosimilar (Mab)/PEG-conjugated gold nanoparticles (MPGs)	- Core size (≈ 5 nm) - 5 K- and 10 K-MPGs were ≈ 20 and 30 nm, respectively)	- MPGs showed a potent antiangiogenic effect that was comparable to that of the Mab solution. - PEG-gold nanoparticles also demonstrated anti-angiogenic activity.	Potent anti-angiogenic activity; no adverse effect on cell proliferation in human endothelial cells	[53]
	Gold nanoparticle-laden contact lenses loaded with timolol, an anti-glaucoma drug	65 ± 5 nm	- In vivo studies displayed prolonged reduction in the intraocular pressure in the rabbits' eyes treated with the gold nanoparticle-laden contact lenses.	Gold nanoparticles enhanced the uptake of timolol from the drug soaking solution to treat glaucoma without altering the critical properties of the contact lens.	[54]

Table 1: *Cont.*

	Composition	Size of Gold Nanoparticles	Remarks	Advantages	References
	Flucytosine-capped gold nanoparticle-loaded liposomes	Optimal formulation F6 135.1 ± 12.0 nm	- The optimal formulation demonstrated significant in vitro antifungal activity against <i>Candida albicans</i> compared with the free flucytosine and gold nanoparticles solutions. - In vivo CT imaging in rabbits' eyes following the administration of F6 demonstrated the highest penetration of the gold nanoparticles within the eyes during the six hours of study. - F6 showed enhanced relative bioavailability that was attributed to the improved residence time of the tested formulation, allowing for greater flucytosine absorption. - In vivo studies in rabbits demonstrated superior antifungal activity of F6 as compared to the flucytosine solution, evidenced by the healing and disappearance of <i>Candida</i> keratitis of infected eyes.	Enhanced antifungal activity, increased ocular penetration, improved bioavailability.	[56]
Nonspherical gold nanoparticles	Gold nanodisks	Diameter of 160 nm	- In an in vitro wound healing assay, the nanodisks suppressed VEGF-induced migration of human retinal microvascular endothelial cells without causing cytotoxicity after 48 h incubation with the highest tested concentrations. - In an oxygen-induced retinopathy mouse model, intravitreal administration of the gold nanodisks (1 and 3 pM) demonstrated a dose-dependent reduction in neovascularization without causing toxicity as confirmed by histological studies.	No evidence of toxicity in retinal integrity and function.	[63]

Table 1: *Cont.*

Composition	Size of Gold Nanoparticles	Remarks	Advantages	References
Pegylated gold nanorods	Length = 77.5 ± 6.5 nm Width = 15.5 ± 1.1 nm Aspect ratio of about 4.9	- PEGylated gold nanorods specifically targeted the cytokinesis process of endothelial cells without inducing DNA damage, cell apoptosis, and autophagy. - Pegylated gold nanorods can be used to interfere with retinal angiogenesis and tumors.	Effective at targeting endothelial cell processes, no apparent DNA damage, no apparent retinal toxicity.	[59]
Molecularly targeted gold nanorods (ICAM2-targeted)	Dimensions of 10 nm × 35 nm	- PTOCT imaging of molecularly targeted gold nanorods allowed for the detection of anti-VEGF-induced changes in the mouse retina in an LCNV model.	Enhanced imaging sensitivity.	[67]
Gold nanostars functionalized with RGD peptide	30 nm	- In vivo, gold nanostars significantly enhanced imaging signals—by up to 17-fold in PAM and 167% in OCT—enabling clear delineation of the choroidal neovascularization margins from the surrounding native tissues.	High photostability, enhanced imaging contrast (PAM, OCT), RGD peptide binds integrin $\alpha v \beta 3$ which is over-expressed in choroidal neovascularization, non-toxic at the tested concentrations.	[69]
Gold nanorods functionalized with the RGD ligand	- Width = 34.17 ± 4.85 nm and length = 103.28 ± 12.07 nm (TEM) - 113 nm (DLS)	- In vivo, intravenous administration of RGD functionalized-gold nanorods into a choroidal neovascularization rabbit model resulted in a 27.2-fold increase in PAM and 171.4% increase in OCT.	Enhanced imaging and visualization in vivo without tissue destruction.	[71]

Although ocular-focused studies are rare, insights from non-ocular applications suggest that nanoparticle morphology strongly influences therapeutic performance. For example, in photothermal therapy, Yang and co-workers investigated gold nanoparticles of three morphologies, including nanospheres, nanorods, and nanostars, all with similar surface modifications [82]. While all gold nanoparticles exhibited photothermal therapeutic effects by converting 808 nm near-infrared laser energy into heat via localized surface plasmon resonance, gold nanostars showed superior photothermal and antitumor activity, likely due to their larger surface area, which provides increased sites for plasmon resonance and enhanced electron trapping on the nanoparticle surface [82]. Similarly, Pakravan and co-authors demonstrated that gold nanostars exhibited lower cytotoxicity, higher cellular uptake, and greater heat generation compared with hollow, rod-shaped, cage-like, spherical, Fe–gold, and Si–gold core–shell gold nanoparticles. Upon photothermal treatment, gold nanostars induced a higher rate of apoptosis in MCF-7 cells, attributed to their substantial heat generation [84]. Functionalization of spherical gold nanoparticles with IR-808 dye enhanced photothermal conversion efficiency fourfold compared with unmodified gold nanoparticles of similar particle size [85].

Nanoparticles with rough surface topology provide more contact points on the cell membrane, thereby enhancing particle–cell interactions and improving cellular internalization. For example, gold nanoparticles with urchin-like morphologies, exhibiting varying Feret lengths and surface topographies, have been designed as ocular drug delivery vehicles for the management of dry eye disease [86]. The rough-surfaced urchin-like morphologies exhibited enhanced cytoadhesion and bioadhesion, particularly in those with longer branches, thereby significantly increasing corneal retention time by 150-fold at 7 days post-instillation compared with smooth gold nanoparticles.

Taken together, these findings indicate that the morphology of gold nanoparticles is a critical determinant of therapeutic efficacy, highlighting the need for further systematic studies to optimize nanoparticle design for ophthalmic applications.

4. Conclusions and Perspectives

The advanced design and synthesis of nanomaterials have contributed to improved early detection and more effective management of ocular diseases. Gold nanoparticles of varying shapes and sizes have been employed in ophthalmology for diagnostic and therapeutic purposes (Figure 9). One of the key advantages of gold nanoparti-

cles is the precise control achievable during their synthesis, which enables fine-tuning of particle size, shape, and surface chemistry. These morphological properties play a crucial role in dictating the cellular uptake, penetration, and biodistribution of gold nanoparticles within ocular tissues. For instance, spherical gold nanoparticles, particularly those with smaller dimensions, exhibit enhanced tissue penetration and have been predominantly investigated for the management of ocular neovascularization and related disorders. In addition to their potential for surface functionalization, their ability to enhance drug stability and delivery supports their use as valuable tools for advancing ocular therapeutic strategies. While spherical gold nanoparticles are used to enhance imaging modalities such as photoacoustic imaging and OCT due to their pronounced localized surface plasmon resonance in the visible spectrum, their peak optical absorption typically lies within the 500–550 nm range, which overlaps significantly with the absorption of endogenous chromophores, particularly hemoglobin. Imaging contrast is often limited, especially in deeper tissues, due to elevated background signals and restricted light penetration. Anisotropic shapes (e.g., rods, cages, or stars) can offer noticeable benefits in imaging and photothermal applications. These anisotropic shapes exhibit tunable plasmonic resonance peaks that can be red-shifted into the NIR region, typically 650–900 nm or even beyond. This spectral window is characterized by minimal absorption and scattering from native tissue components, enabling superior imaging depth and contrast in photoacoustic and optical coherence tomography (OCT) applications. In addition, rough surface topologies, such as urchin-like gold nanoparticles, can enhance cellular adhesion and prolong corneal residence time, thereby improving cellular internalization. This tunability, together with enhanced functional performance, makes nonspherical gold nanoparticles an attractive tool for targeted molecular imaging, image-guided therapy, and real-time diagnostics, particularly in applications that require deep tissue penetration (e.g., tumor detection, vascular imaging, and monitoring of inflammation).

Several clinical trials involving gold nanoparticle platforms have been reported; however, no ocular applications have yet advanced to clinical trials. A better understanding of the behavior of gold nanoparticles within the ocular environment, along with the influence of their morphology on pharmacological activity, enables significant advancements in the rational design of nanomaterials. This knowledge supports the tuning of nanoparticle structure and morphology to improve therapeutic outcomes and address current limitations in ocular drug delivery. The safety, scalability, and reproducibility of ther-

apeutic and diagnostic gold nanoparticles are critical parameters that must be addressed for successful clinical translation and commercialization. Although several studies have reported the use of gold nanoparticles as contrast agents for OCT imaging in the eye, further investigations are required to ensure their safety. In particular, comprehensive biocompatibility and toxicity assessments are nec-

essary prior to clinical translation. In vivo tracking, long-term accumulation and safety assessment, along with evaluation of clearance pathways and retinal toxicity risks, are also critical considerations for the development of next-generation nanotherapeutics and diagnostic platforms for ocular diseases.

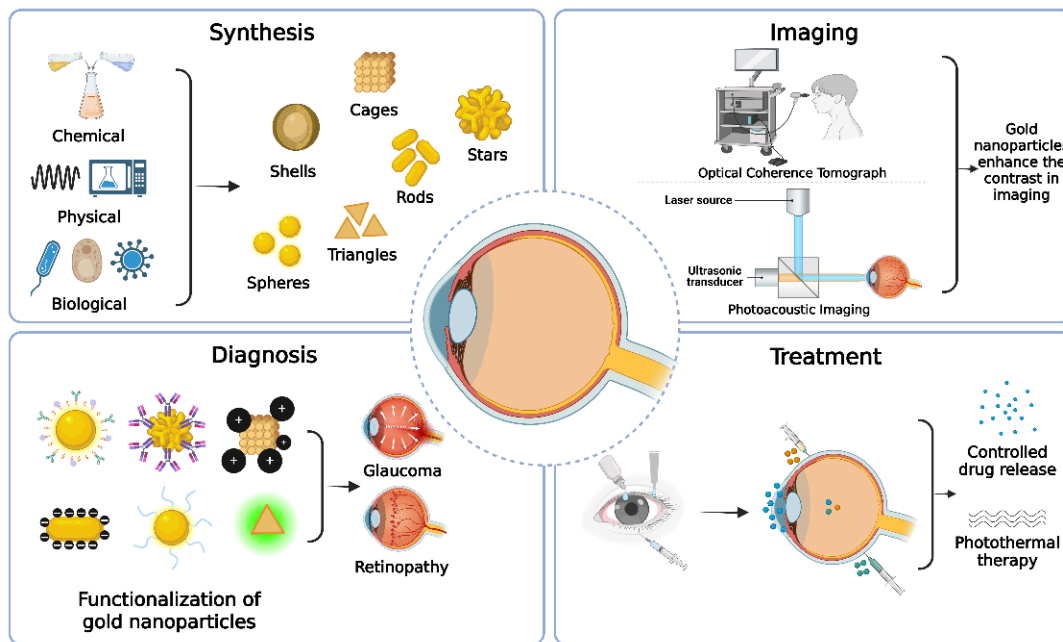


Figure 9: Gold nanoparticles of various shapes and sizes are exploited for multiple ocular applications. Created by BioRender.com.

List of Abbreviations

CD44	Cluster of Differentiation 44
CNV	Choroidal Neovascularization
CT	Computed Tomography
CTAB	Cetyltrimethylammonium bromide
DLS	Dynamic Light Scattering
DNA	Deoxyribonucleic Acid
ICAM2	Intercellular Adhesion Molecule 2
LCNV	Laser-Induced Choroidal Neovascularization
MPGs	PEG-Conjugated Gold Nanoparticles
NIR	Near-Infrared
OCT	Optical Coherence Tomography
PAM	Photoacoustic Microscopy
PEG	Polyethylene Glycol
PPTT	Plasmonic Photothermal Therapy
PTOCT	Photothermal Optical Coherence Tomography
RGD	Arginine-Glycine-Aspartic Acid
TEM	Transmission Electron Microscopy
VEGF	Vascular Endothelial Growth Factor
WHO	WorldHealthOrganization

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Conflicts of Interest

The authors declare no conflicts of interest.

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