·Review·

Nanoparticles in the ocular drug delivery

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Foundation items: Norman Bethune Program of Jilin University, China (No.2012230); Research Fund of Jilin Provincial Science and Technology Department (International Cooperation Item, No. 20120726)

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Received: 2013-03-15 Accepted: 2013-05-29

Abstract

• Ocular drug transport barriers pose a challenge for drug delivery comprising the ocular surface epithelium, the tear film and internal barriers of the blood-aqueous and blood-retina barriers. Ocular drug delivery efficiency depends on the barriers and the clearance from the choroidal, conjunctival vessels and lymphatic. Traditional drug administration reduces the clinical efficacy especially for poor water soluble molecules and for the posterior segment of the eye. Nanoparticles (NPs) have been designed to overcome the barriers, increase the drug penetration at the target site and prolong the drug levels by few internals of drug administrations in lower doses without any toxicity compared to the conventional eye drops. With the aid of high specificity and multifunctionality, DNA NPs can be resulted in higher transfection efficiency for gene therapy. NPs could target at cornea, retina and choroid by surficial applications and intravitreal injection. This review is concerned with recent findings and applications of NPs drug delivery systems for the treatment of different eye diseases.

• KEYWORDS: nanoparticles; eye; drug delivery

DOI:10.3980/j.issn.2222-3959.2013.03.25

Zhou HY, Hao JL, Wang S, Zheng Y, Zhang WS. Nanoparticles in the ocular drug delivery. *Int J Ophthalmol* 2013;6(3):390-396

INTRODUCTION

Various efforts have been made to improve the bioavailability and the drug release and absorbing rate from formulations or dosage forms. Engineered nanodevices and nanostructures operate human biological systems at the single-cell and molecular level [1]. Nanoparticles (NPs) with size range from 10nm to 1 000nm improved topical passage of large, poorly water-soluble molecules through the barriers of ocular system [2]. Superficial barriers impede direct and systemic drug access to the specific site of action. Drug loaded NPs favorable biological properties include prolonging the residence time of eye drops and decreasing toxicity and high ability of drug penetration into the deeper layers of the ocular structure and the aqueous humor minimizing precorneal drug loss by the rapid tear fluid turnover [3-4]. The techniques were planned to transform NPs from lipophilic to hydrophilic and downregulated irritant to the eye. Some methods loaded with NPs could be very useful for extended delivery of ophthalmic drugs [5-7]. NPs deliver ocular drugs to the target sites were applied in the treatments of many eye diseases as follows[1] (Figure 1).

GLAUCOMA

Glaucoma leads to vision loss even blindness. The progressions of drug delivery systems can lead to greater treatment options and preservation of vision in glaucoma [8]. New drugs were anticipated effective drug bioavailability and sustained time without toxic effects.

New Methods were Explored to Enhance the Drug Delivery Efficient and Patient Adherence Drug delivery systems have the potential to improve patient adherence, reduce side effects, increase efficacy, and preserve sight for glaucoma patients [8]. Mucus-penetrating particle topical administration nanotechnology could improve the effectiveness of approaches for glaucoma [9]. Hybrid polyamidoamine (PAMAM) dendrimer hydrogel/poly (lactic-co-glycolic acid) (PLGA) nanoparticle platform (HDNP) for codelivery of two traditional antiglaucoma drugs brimonidine and timolol maleate showed no cytotoxic effect and prolonged residence time with slowly released period thus enhancing drug bioavailability in glaucoma treatments [10]. Brimonidine tartrate (BT) loaded chitosan (CS) NPs prepared by inducing the ionic gelation upon addition of sodium tripolyphosphate (TPP) could help to reduce dosage frequency by sustained drug release in the treatment of glaucoma [11]. Methazolamide, bounding to CaP NPs prolong the intraocular pressure (IOP)-lowering effect duration time, has been shown to be useful in the local treatment of glaucoma [12]. Hyaluronic acid modified chitosan NPs (CS-HA-NPs) may be a promising carrier for glaucoma drug delivery [13]. Positively-charged pilocarpine HCl-loaded polymeric and lipid NPs by quasi-emulsion solvent evaporation technique was potent for glaucoma[14].

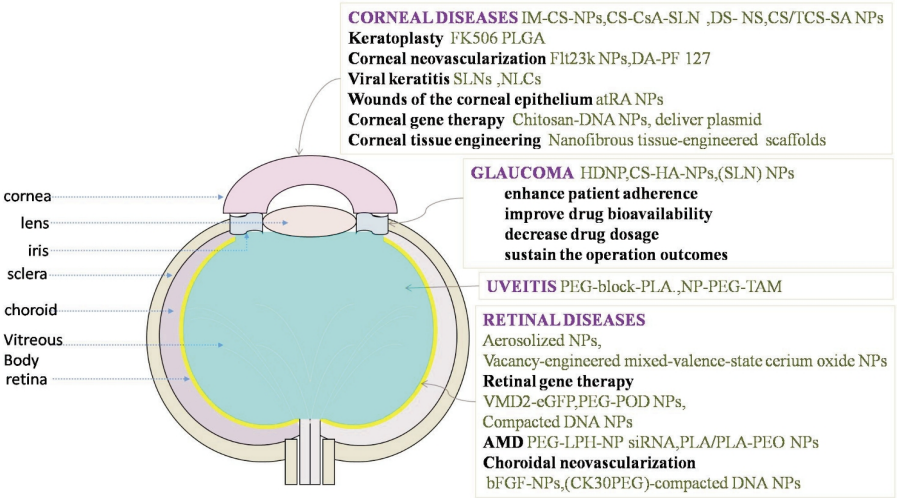

Figure 1 Nanoparticles in the ocular drug delivery.

Some Traditional Antiglaucoma Administrations were Cooperated with Nanomedicine Approach to Improve Drug Bioavailability and Decrease Drug Dosage Formulation of dorzolamide hydrochloride and Methazolamide- loaded solid lipid NPs (SLN) in a nanoemulsion form offers a more intensive treatment of glaucoma, a decrease in the number of applications per day, and a better patient compliance compared to conventional eye drops [4, 15]. Eudragit NPs of brimonidine tartrate made by double emulsion-solvent evaporation technique prolong the drug release *in vitro* and prolong IOP reduction efficacy *in vivo*. This was potential for the treatment of open-angle glaucoma [16]. Nanovesicles were developed for brimonidine tartrate by film hydration technique and dispersed in viscous carbopol solution had the potential in reducing dosing frequency and could improve patient compliance [6]. Surface-modified SLNs containing timolol with phospholipid formulated by melt emulsification with high-pressure homogenization, could provide an efficient way of improving ocular bioavailability of timolol hydrogen maleate [17]. Acetazolamide-loaded cationic nanosized emulsion rather than anionic and neutral-charged emulsions could be suitable for eye drop in the treatment of glaucoma [18]. Seventeen dorzolamide hydrochloride nanoemulsions showed stable physicochemical properties and were nonirritant. The nanoemulsions can offer a intensive treatment of glaucoma[4].

Some Technique was Planned to Sustain the Operation Outcomes LDL-mitomycin C-chitosan NPs can be applicable to anti-scarring therapy during excessive conjunctival wound healing[19].

CORNEAL DISEASES

SLNs prepared with a mixture of stearic acid and compritol would be a good ocular drug delivery system considering the smaller particle size, particle size stability, and physiologically tolerable components [20]. Poly (D,L-lactide-co-glycolide) nanospheres incorporating flurbiprofen were prepared by the solvent displacement technique, this kind of NPs enhanced drug penetration [21]. The Cyclosporine A (CsA)-loaded or fluorescein-marked nanocarriers composed of Precifac ATO 5 and Miglyol 840 (as liquid lipid) were prepared by melting-emulsion technology. Lipid carriers (NLCs) was biocompatible and potential [22]. Indomethacin (IM)-Chitosan (CS)-nanoemulsion showed clearer healing of corneal chemical ulcer compared with NPs preparation and high level of IM in inner ocular structure thereby increasing drug delivery efficiency [23]. Positively charged fluorescent NPs by using the technique of non-invasive iontophoresis had showed better penetration abilities into inner ocular tissues [24]. CsA loaded SLN associated with CS were prepared by high shearhomogenization and ultrasound methods. CS-CsA-SLN were biocompatible and higher permeation in cornea and in RCE cell lines, pointing out the possibility of CsA targeting to the cornea [25-27]. SLN of baicalin was prepared by emulsification/ultrasonication method. This kind of NPs can retained better drug entity and ocular irritation. High concentration of baicalin can be detected in aqueous humors [28]. Polymeric nanoparticle suspensions (NS) prepared by emulsion and solvent evaporation technique were loaded with diclofenac sodium (DS). NS showed a extended-release profile of DS and no irritant effect on cornea and iris thus can be suitable inert carrier for ophthalmic drug delivery [29]. Chitosan/thiolated chitosan-sodium alginate NPs (CS/TCS-SA NPs) could deliver greater amounts of drugs into HCE cells *in vitro* and cornea *in vivo*, suggesting they have good potential for ocular drug delivery applications [30]. Poly (D, L-lactide-co-glycolide) withpoly (ethylene glycol) nanospheres (NSs) incorporating flurbiprofen (FB) penetrate corneal epithelium through atranscellular pathway [31]. Gatifloxacin involved in polyguanidilyated translocators nanodendrimers increased GFX solubility, rapid entrance into human corneal epithelial cells. Aqueous humor andvitreous humor drug levels retained longer[32]. Fluorescent Hyaluronic acid-chitosan NPs prepared by ionotropicgelation using fluoresceinamine-labeled

hyaluronic acid and resuspended inbuffer were compatible. Corneal tissue morphology and functionality did not show any changes[33]. Chitosan coated PLA Nano-carrier for topical ocular applications incorporated with 5-fluorouracil showed higher concentrations in aqueous and vitreous humor than free solution and better permeation efficiency for cornea[34].

Keratoplasty FK506 is an immunosuppressant. FK506 nanospheres prepared by using a biodegradable poly (lactic-co-glycolic acid) copolymer (PLGA) could suppress corneal graft rejection and prolong the allograft survival time[35].

Corneal Neovascularization Corneal neovascularization is a sight-threatening condition usually associated with disorders of the ocular surface. NPs delivering plasmids expressing Flt23k (an anti-VEGF intraceptor) have a significant effect on decreasing corneal neovascularization and lymphangiogenesis, resulting in increased graft survival in penetrating keratoplasty [36]. The core/shell nanoparticle system with a photo-crosslinked shelllayer by using a lecithin liposome as the core and pluronic F 127 diacrylate (DA-PF 127) as the shell layer increased structural stability of NPs. The core/shell nanoparticle loaded with VEGF resulted in more efficient in the therapy of new blood vesselformation[37]. Celastrol-loadedpoly (ethyleneglycol) -block-poly (-capro-lactone) nanopolymeric micelles was planned to improve the hydrophilicity of celastrol and significantly inhibited suture-induced corneal neovascularization [38].

Viral Keratitis SLNs and nanostructured lipid carriers (NLCs) were prepared by the modified hot oil in watermicroemuslion method, which have the potential to be developed further as ocular drug delivery systems for acyclovir[39].

Wounds of the Corneal Epithelium Inorganically-coated all-trans retinoic acid (atRA) NPs promotes wound healing and should be considered for the treatment of wounds of the corneal epithelium[40].

Developments of NPs in the Therapy of Corneal Diseases

Corneal gene therapy Gene therapy offers a promising alternative for the treatment of ocular diseases. Nanomedicine improves the transfection efficiency. Chitosan-DNA NPs has the proper nanoparticle size and positive zeta potential charge and can be pharmaceuticals for corneal gene therapy. Corneal fibroblasts can express the transgene green fluorenscent protein [41]. Hybridcationized gelatin NPs which were developed by the ionic gelation technique contained polyanions (chondroitin sulfateor dextran sulfate) can transfect ocular epithelial cells. NPs are effective vehicles for gene therapy and can increase the MUC5AC concentration in the ocular surface[42]. Oligodeoxynucleotides can be incorporated into poly (D,L-lactic-co-glycolic acid) NPs which were prepared by the method of double emulsion solvent evaporate and can transport into cells due to polymer erosion [43]. Hybrid NPs composed of cationizedgelatin and the polyanions CS and DS decreases the *in vitro* toxicity to corneal cells and let the NPs safer and more efficient [44, 45]. Nanoparticle made of two bioadhesive polysaccharides, hyaluronic acid (HA) and CS, deliver plasmid DNA to the cornea and conjunctiva[46]. 2-kDa polyethylenimine conjugated to gold NPs (PEI2-GNPs) can get nitrogen-to-phosphorus ratios of up to 180 exhibited significant transgene delivery in the human cornea without any toxicity effect and can be uptaken through all the layers of cornea with gradual clearance[47]. Levofloxacin encapsulatedpoly (lactic-co-glycolic acid) NPs showed the nonirritant efficacy and longer retaining over precorneal area. The NPs can be measured of high entrapment efficiency and can be proved to be a stable formulation [48]. Self-assembled liquid crystalline NPs (cubosomes) for dexamethasone (DEX) increase the permeability and preocular retention. Good biocompatibility of DEX cubosomes were demonstrated by corneal cross-section[49].

Corneal tissue engineering SLNs incorporated with diclofenac sodium (DNa) were prepared with a combination of homolipid from goat and phospholipid. The permeation of DNa through the bio-engineered human cornea was improved [50]. Nanofibers prepared by industrial scale needleless technology were used as cell carriers for the regeneration of theinjured cornea. Nanofibrous materials can be tissue-engineered scaffolds for the corneal cells adhesion and mimic the native extracellular matrix[51].

UVEITIS

Autoimmune uveitis is an occoecatio disease that targets the posterior part of the eye. More efficient modes of NPs drug delivery were applied in the treatments of immunological autoimmune uveitis with less side effects [52]. Nanocarriers permit the non-steroidal anti-inflammatory drug indomethacin to reach inner eye structures using the transmucosal route[2]. Intravitreal injection of dexamethasone (DEX)-loaded poly (lactic acid-co-glycolic acid) NPs can sustained DEX concentrations for a long time appearing in all the layers of the eye ball thus can be used for the treatments of posterior segment diseases [53]. The therapeutic effects of betamethasone phosphate (BP) encapsulated in biocompatible and biodegradable blended NPs of poly (lactic acid) (PLA) homopolymers and PEG-block-PLA copolymers (stealth nanosteroids) reduced the clinical scores of rats with experimental autoimmune uveoretinitis (EAU) and decreased the inflammatory cytokines in the retina of EAU by prolonged blood circulation [54]. NPs prepared by using sialyl-Lewis X conjugated liposome as a site-directed delivery system containing dexamethasone showed selective targeting to the autoimmune uveoretinitis[55]. Poly(lactic acid) NPs encapsulating BP was injected intravenously to EAU rats. Injected NPs remained for 7 days with reducing infiltration of activated T-cells and macrophages in addition

to the hypertrophy of Müller cells [56]. Polyethylene glycol (PEG)-coated NPs incorporated tamoxifen (NP-PEG-TAM) were injected into the vitreous cavity of rats with retinal soluble antigen (S-Ag)-induced EAU. Expressions of MHC class II (+) inflammatory cells, TNF-alpha, IL-1beta and RANTES mRNA decreased by the therapy [57]. NPs delivery system may lead to a new therapeutic strategy in controlling intraocular inflammation.

RETINAL DISEASES

The blood-retina barrier and sclera prevent high molecular weight drugs to reach the tight junctions in the retinal pigment epithelium with limited transcellular diffusion after systemic or topical application[58,59]. Intraocular drug delivery systems that achieve longer duration of pharmacological effect with lower administration frequency are urgently needed[60]. Intravitreal nanogold showed no signs of retinal or optic nerve toxicity during histologic examination by light microscopy[61]. Aerosolized NPs was used in the gas phase of vitrectomy peforming antimetabolites for modulation of proliferative vitreoretinopathy, antimicrobial agents for endophthalmitis, antiangiogenic compounds for vasoproliferative disorders, corticosteroid delivery, and other pharmacotherapies directed at the retina and choroid [62]. Vacancy-engineered mixed-valence-state cerium oxide NPs (nanoceria particles) scavenge reactive oxygen intermediates as a direct therapy for multiple diseases suggests that they may represent a unique platform technology [63]. It is a very important application of NPs presented here and now a novel drug Ozurdex (dexamethasone intravitreal implant) had been under investigation in a clinical trial for the treatment of vitreoretinal disorders[64-66].

Retinal Gene Therapy Subretinal injections of rhodamine labeled NPs using an RPE-specific reporter vector (VMD2-eGFP) can efficiently deliver genes to the RPE [67]. NPs can be prepared by interaction of cationic polymers with DNA, which facilitate cellular uptake, endolysosomal escape and nuclear entry through active mechanisms [68]. US and/or MBs could be used safely to enhance the delivery of NPs loading siRNA to rat RPE cells[69]. A novel synthetic peptide for ocular delivery was modified using poly (ethylene) glycol (PEG-POD) and used to compact DNA into NPs. The NPs was then injected to the subretinal space with no toxicity and can protect plasmid DNA from digestion [70]. After the subretinal injection of goat IgG-adsorbed GNPs, GNPs located in the outer segments and in the lysosomes in the RPE without cytotoxicity. Goat IgG was successfully delivered into photoreceptor cells and RPE using GNPs. This might be an alternative drug delivery method to photoreceptors and RPE [71]. The human serum albumin NP developed by a desolvation-crosslinking method offers a very promising approach for nonviral gene delivery to the retina[72]. SLNs revealed a delay in cell uptake of the vectors in ARPE-19 cells, this cell line hampers the entrance of DNA into the nucleus [73]. Compacted DNA NPs treatment strategy appears to be clinically viable and provides a highly efficient non-viral technology to safely deliver and express nucleic acids in the retina and other ocular tissues[74].

Age-Related Macular Degeneration PEGylated liposome-protamine-hyaluronic acid NPs (PEG-LPH-NP) loaded with siRNA (PEG-LPH-NP-S) will be promising for the treatment of choroidal neovascularization [75]. Cerium oxide NPs intravitreal injection inhibit: the reactive oxygen species rise and the formation of intraretinal and subretinal neovascular lesions. This character will be potential for treatment of neurodegenerative diseases such as age-related macular degeneration (AMD) and diabetic retinopathy [76]. Cerium oxide NPs, which had neuroprotective catalytic activities was potential for the treatment of inherited retinal degeneration[77]. Nanoparticle-mediated delivery of plasminogen kringle 5 (K5) reduced vascular permeability and the expressions of VEGF, TNF-α, ICAM-1, β-catenin, MCP-1 and TNF-α.K5 mediates a sustained inhibitory effect on choroidal neovascularization and thus has therapeutic potential for AMD and diabetic retinopathy[78-79]. Gold nanoparticle (GNP) could inhibit retinal neovascularization by intravitreal injection. GNP inhibit VEGF induced retinal microvascular endothelial cells proliferation and new vessel formation[80-82]. SLNs may facilitate continuous, noninvasive treatment of patients with retinitis pigmentosa and other retinal pathologies, increased photoreceptor survival, preserved photoreceptor morphology, and extended the ability of the retina to respond to light as assessed by electroretinography[83]. Microneedles can be a potent technique to deliver nanoparticle to the posterior eye[84]. 20nm gold NPs could be an alternative for drug delivery across the blood-retinal barrier (BRB), distributed in all retinal layers [85]. Polylactic acid/polylactic acid-polyethylene oxide NPs (PLA/PLA-PEO) encapsulating the water-soluble integrin-antagonist peptide, C16Y (C16Y-NP).

Choroidal Neovascularization Choroidal neovascularization originated from AMD was smaller by injection of NPs of biodegradable polymers without toxicity effects [86]. Intravitreal injection of basic fibroblast growth factor-impregnated NPs (bFGF-NPs) prevent photoreceptor degeneration by inhibiting apoptosis in rat retina [87]. Subretinal delivery of polyethylene glycol-substituted lysine peptide (CK30PEG)-compacted DNA NPs results in efficient gene expression in retinal cells. Inflammatory cytokines monocyte chemotactic protein-1, chemokine KC, macrophage marker F4/80 or myeloid marker myeloperoxidase showed at control levels post injection [88]. NPs intravitreal injection was appropriate for the treatments of retinal diseases.

Poisonous Effect on Retina The water-soluble nanoparticle hydroxylated fullerene [fullerol, nano-C60(OH)(22-26)] was cytotoxic toward hRPE cells and retinal damage maintained

in concentration higher than 10mmol/L [89]. Anti-angiogenic potential of silver NPs, produced by Bacillus licheniformis inhibit Bovine retinal endothelial cells survival by enhancement in caspase-3 activity and DNA ladders formation. Magnetite NPs coated with triblock copolymers containing polyethylenoxide tail lengths of above 2kDa are biocompatible and appropriate for *in vivo* application. The NPs with polyethylenoxide less than that will be toxic [90]. Implications or safety issue are always a big issue for therapeutic application of "foreigners" in eye and other organs.The application of the structure-toxicity paradigm to nanomaterials represents a promising approach to decrease its side effects. The future possibilities of nanoparticles as drug delivery systems will be hypotoxic[91,92].

CHALLENGES OF NPs

In this review, we introduce the NPs applications in different eye diseases. Although nanoparticulate drug delivery was one of the most promising technologies to overcome poor stability in physiological medium and delivering them across biological barriers [93].NPs as drug or gene carriers had no influence on cornea, iris and even retina. Analysis for evaluation of the biological effects needs further observations. Nanomedicine gain Gold NPs requires heating and long incubation times are needed[94].NPs incorporation of high amounts of DNA will be challenges for gene delivery[95]. The surfaces of insoluble particles and factors released by soluble NPs will interact with biological systems[96]. Rational design of nanomaterials needs to be modified. Future work should focus on trialing combinations of additives to enhance favourable properties. Clinical development is ongoing and it will be interesting what benefits can these innovative drugs provide for patients[97,98].

REFERENCES

1 Zarbin MA, Montemagno C, Leary JF, Ritch R. Nanotechnology in ophthalmology. *Can J Ophthalmol* 2010;45(5):457-476

2 Diebold Y, Calonge M. Applications of nanoparticles in ophthalmology. *Prog Retin Eye Res* 2010;29(6):596-609

3 Kesavan K, Balasubramaniam J, Kant S, Singh PN, Pandit JK. Newer approaches for optimal bioavailability of ocularly delivered drugs: review. *Curr Drug Deliv* 2011;8(2):172-193

4 Ammar HO, Salama HA, Ghorab M, Mahmoud AA. Nanoemulsion as a potential ophthalmic delivery system for dorzolamide hydrochloride. *AAPS Pharm Sci Tech* 2009;10(3):808-819

5 Baba K, Tanaka Y, Kubota A, Kasai H, Yokokura S, Nakanishi H, Nishida K. A method for enhancing the ocular penetration of eye drops using nanoparticles of hydrolyzable dye. *J Control Release* 2011;153 (3): 278-287

6 Maiti S, Paul S, Mondol R, Ray S, Sa B. Nanovesicular formulation of brimonidine tartrate for the management of glaucoma: *in vitro* and *in vivo* evaluation. *AAPS Pharm Sci Tech* 2011;12(2):755-763

7 Jung HJ, Chauhan A. Temperature sensitive contact lenses for triggered ophthalmic drug delivery. *Biomaterials* 2012;33(7):2289-2300

8 Lavik E, Kuehn MH, Kwon YH. Novel drug delivery systems for glaucoma. *Eye (Lond)* 2011;25(5):578-586

9 Ensign LM, Schneider C, Suk JS, Cone R, Hanes J. Mucus penetrating nanoparticles: biophysical tool and method of drug and gene delivery. *Adv Mater* 2012;24(28):3887-3894

10 Yang H, Tyagi P, Kadam RS, Holden CA, Kompella UB. Hybrid Dendrimer hydrogel/PLGA nanoparticle platform sustains drug delivery for one week and antiglaucoma effects for four days following one-time topical administration. *ACS Nano* 2012;6(9):7595-7606

11 Singh KH, Shinde UA. Chitosan nanoparticles for controlled delivery of brimonidine tartrate to the ocular membrane. *Pharmazie* 2011;66 (8): 594-599

12 Chen R, Qian Y, Li R, Zhang Q, Liu D, Wang M, Xu Q. Methazolamide calcium phosphate nanoparticles in an ocular delivery system. *Yakugaku Zasshi* 2010;130(3):419-424

13 Wadhwa S, Paliwal R, Paliwal SR, Vyas SP. Hyaluronic acid modified chitosan nanoparticles for effective management of glaucoma: development, characterization, and evaluation. *J Drug Target* 2010;18(4):292-302

14 Lütfi G, Müzeyyen D. Preparation and characterization of polymeric and lipid nanoparticles of pilocarpine HCl for ocular application. *Pharm Dev Technol* 2013;18(3):701-709

15 Li R, Jiang S, Liu D, Bi X, Wang F, Zhang Q, Xu Q. A potential new therapeutic system for glaucoma: solid lipid nanoparticles containing methazolamide. *J Microencapsul* 2011;28(2):134-141

16 Bhagav P, Upadhyay H, Chandran S. Brimonidine tartrate-eudragit long-acting nanoparticles: formulation, optimization, *in vitro* and *in vivo* evaluation. *AAPS PharmSciTech* 2011;12(4):1087-1101

17 Attama AA, Reichl S, Müller-Goymann CC. Sustained release and permeation of timolol from surface-modified solid lipid nanoparticles through bioengineered human cornea. *Curr Eye Res* 2009;34(8):698-705

18 Tamilvanan S, Kumar BA. Influence of acetazolamide loading on the (*in vitro*) performances of non-phospholipid-based cationic nanosized emulsion in comparison with phospholipid-based anionic and neutral-charged nanosized emulsions. *Drug Dev Ind Pharm* 2011;37 (9): 1003-1015

19 Shao T, Li X, Ge J. Target drug delivery system as a new scarring modulation after glaucoma filtration surgery. *Diagn Pathol* 2011;6:64

20 Kalam MA, Sultana Y, Ali A, Aqil M, Mishra AK, Chuttani K. Preparation, characterization, and evaluation of gatifloxacin loaded solid lipid nanoparticles as colloidal ocular drug delivery system. *J Drug Target* 2010;18(3):191-204

21 Vega E, Gamisans F, García ML, Chauvet A, Lacoulonche F, Egea MA. PLGA nanospheres for the ocular delivery of flurbiprofen: drug release and interactions. *J Pharm Sci* 2008;97(12):5306-5317

22 Shen J, Sun M, Ping Q, Ying Z, Liu W. Incorporation of liquid lipid in lipid nanoparticles for ocular drug delivery enhancement. *Nanotechnology* 2010;21(2):025101

23 Badawi AA, El-Laithy HM, El Qidra RK, El Mofty H, El dally M. Chitosan based nanocarriers for indomethacin ocular delivery. *Arch Pharm Res* 2008;31(8):1040-1049

24 Eljarrat-Binstock E, Orucov F, Aldouby Y, Frucht-Pery J, Domb AJ. Charged nanoparticles delivery to the eye using hydrogel iontophoresis. *J Control Release* 2008;126(2):156-161

25 Gokce EH, Sandri G, Bonferoni MC, Rossi S, Ferrari F, Güneri T, Caramella C. Cyclosporine A loaded SLNs: evaluation of cellular uptake and corneal cytotoxicity. *Int J Pharm* 2008;364(1):76-86

26 Yenice I, Mocan MC, Palaska E, Bochot A, Bilensoy E, Vural I, Irkeç M, Hincal AA. Hyaluronic acid coated poly-epsilon-caprolactone nanospheres deliver high concentrations of cyclosporine A into the cornea. *Exp Eye Res* 2008;87(3):162-167

27 Sandri G, Bonferoni MC, Gökçe EH, Ferrari F, Rossi S, Patrini M, Caramella C. Chitosan-associated SLN: *in vitro* and *ex vivo*

characterization of cyclosporine A loaded ophthalmic systems. *J Microencapsul* 2010;27(8):735-746

28 Liu Z, Zhang X, Wu H, Li J, Shu L, Liu R, Li L, Li N. Preparation and evaluation of solid lipid nanoparticles of baicalin for ocular drug delivery system *in vitro* and *in vivo*. *Drug Dev Ind Pharm* 2011;37(4):475-481

29 Agnihotri SM, Vavia PR. Diclofenac-loaded biopolymeric nanosuspensions for ophthalmic application. *Nanomedicine* 2009;5 (1): 90-95

30 Zhu X, Su M, Tang S, Wang L, Liang X, Meng F, Hong Y, Xu Z. Synthesis of thiolated chitosan and preparation nanoparticles with sodium alginate for ocular drug delivery. *Mol Vis* 2012;18:1973-1982

31 Vega E, Egea MA, Calpena AC, Espina M, García ML. Role of hydroxypropyl-β-cyclodextrin on freeze-dried and gamma-irradiated PLGA and PLGA-PEG diblock copolymer nanospheres for ophthalmic flurbiprofen delivery. *Int J Nanomedicine* 2012;7:1357-1371

32 Durairaj C, Kadam RS, Chandler JW, Hutcherson SL, Kompella UB. Nanosized dendritic polyguanidilyated translocators for enhanced solubility, permeability, and delivery of gatifloxacin. *Invest Ophthalmol Vis Sci* 2010; 51(11):5804-5816

33 Contreras-Ruiz L, de la Fuente M, García-Vázquez C, Sáez V, Seijo B, Alonso MJ, Calonge M, Diebold Y. Ocular tolerance to a topical formulation of hyaluronic acid and chitosan-based nanoparticles. *Cornea* 2010;29 (5): 550-558

34 Nagarwal RC, Singh PN, Kant S, Maiti P, Pandit JK. Chitosan coated PLA nanoparticles for ophthalmic delivery: characterization, *in-vitro* and *in-vivo* study in rabbit eye. *J Biomed Nanotechnol* 2010;6(6):648-657

35 Fei WL, Chen JQ, Yuan J, Quan DP, Zhou SY. Preliminary study of the effect of FK506 nanospheric-suspension eye drops on rejection of penetrating keratoplasty. *J Ocul Pharmacol Ther* 2008;24(2):235-244

36 Cho YK, Uehara H, Young JR, Tyagi P, Kompella UB, Zhang X, Luo L, Singh N, Archer B, Ambati BK. Flt23k nanoparticles offer additive benefit in graft survival and anti-angiogenic effects when combined with triamcinolone. *Invest Ophthalmol Vis Sci* 2012;53(4):2328-2336

37 Choi WI, Yoon KC, Im SK, Kim YH, Yuk SH, Tae G. Remarkably enhanced stability and function of core/shell nanoparticles composed of a lecithin core and a pluronic shell layer by photo-crosslinking the shell layer: *in vitro* and *in vivo* study. *Acta Biomater* 2010;6(7):2666-2673

38 Li Z, Yao L, Li J, Zhang W, Wu X, Liu Y, Lin M, Su W, Li Y, Liang D. Celastrol nanoparticles inhibit corneal neovascularization induced by suturing in rats. *Int J Nanomedicine* 2012;7:1163-1173

39 Seyfoddin A, Al-Kassas R. Development of solid lipid nanoparticles and nanostructured lipid carriers for improving ocular delivery of acyclovir. *Drug Dev Ind Pharm* 2013;39(4):508-519

40 Hattori M, Shimizu K, Katsumura K, Oku H, Sano Y, Matsumoto K, Yamaguchi Y, Ikeda T. Effects of all-trans retinoic acid nanoparticles on corneal epithelial wound healing. *Graefes Arch Clin Exp Ophthalmol* 2012; 250(4):557-563

41 Klausner EA, Zhang Z, Chapman RL, Multack RF, Volin MV. Ultrapure chitosan oligomers as carriers for corneal gene transfer. *Biomaterials* 2010; 31(7):1814-1820

42 Konat Zorzi G, Contreras-Ruiz L, Párraga JE, López-García A, Romero Bello R, Diebold Y, Seijo B, Sánchez A. Expression of MUC5AC in ocular surface epithelial cells using cationized gelatin nanoparticles. *Mol Pharm* 2011;8(5):1783-1788

43 Chen YS, Alany RG, Young SA, Green CR, Rupenthal ID. *In vitro* release characteristics and cellular uptake of poly (D,L-lactic-co-glycolic acid) nanoparticles for topical delivery of antisense oligodeoxynucleotides. *Drug Deliv* 2011;18(7):493-501

44 Zorzi GK, Párraga JE, Seijo B, Sánchez A. Hybrid nanoparticle design based on cationized gelatin and the polyanions dextran sulfate and chondroitin sulfate for ocular gene therapy. *Macromol Biosci* 2011;11 (7): 905-913

45 de la Fuente M, Seijo B, Alonso MJ. Novel hyaluronic acid-chitosan nanoparticles for ocular gene therapy. *Invest Ophthalmol Vis Sci* 2008;49 (5):2016-2024

46 Contreras-Ruiz L, de la Fuente M, Párraga JE, López-García A, Fernández I, Seijo B, Sánchez A, Calonge M, Diebold Y. Intracellular trafficking of hyaluronic acid-chitosan oligomer-based nanoparticles in cultured human ocular surface cells. *Mol Vis* 2011;17:279-290

47 Sharma A, Tandon A, Tovey JC, Gupta R, Robertson JD, Fortune JA, Klibanov AM, Cowden JW, Rieger FG, Mohan RR. Polyethylenimine-conjugated gold nanoparticles: Gene transfer potential and low toxicity in the cornea. *Nanomedicine* 2011;7(4):505-513

48 Gupta H, Aqil M, Khar RK, Ali A, Bhatnagar A, Mittal G. Biodegradable levofloxacin nanoparticles for sustained ocular drug delivery. *J Drug Target* 2011;19(6):409-417

49 Gan L, Han S, Shen J, Zhu J, Zhu C, Zhang X, Gan Y. Self-assembled liquid crystalline nanoparticles as a novel ophthalmic delivery system for dexamethasone: Improving preocular retention and ocular bioavailability. *Int J Pharm* 2010;396(1-2):179-187

50 Attama AA, Reichl S, Müller-Goymann CC. Diclofenac sodium delivery to the eye: *in vitro* evaluation of novel solid lipid nanoparticle formulation using human cornea construct. *Int J Pharm* 2008;355 (1-2): 307-313

51 Kubinová S, Syková E. Nanotechnologies in regenerative medicine. *Minim Invasive Ther Allied Technol* 2010;19(3):144-156

52 Gomes Bittencourt M, Sepah YJ, Do DV, Agbedia O, Akhtar A, Liu H, Akhlaq A, Annam R, Ibrahim M, Nguyen QD. New treatment options for noninfectious uveitis. *Dev Ophthalmol* 2012;51:134-161

53 Zhang L, Li Y, Zhang C, Wang Y, Song C. Pharmacokinetics and tolerance study of intravitreal injection of dexamethasone-loaded nanoparticles in rabbits. *Int J Nanomedicine* 2009;4:175-183

54 Sakai T, Ishihara T, Higaki M, Akiyama G, Tsuneoka H. Therapeutic effect of stealth-type polymeric nanoparticles with encapsulated betamethasone phosphate on experimental autoimmune uveoretinitis. *Invest Ophthalmol Vis Sci* 2011;52(3):1516-1521

55 Hashida N, Ohguro N, Yamazaki N, Arakawa Y, Oiki E, Mashimo H, Kurokawa N, Tano Y. High-efficacy site-directed drug delivery system using sialyl-Lewis X conjugated liposome. *Exp Eye Res* 2008;86 (1): 138-149

56 Sakai T, Kohno H, Ishihara T, Higaki M, Saito S, Matsushima M, Mizushima Y, Kitahara K. Treatment of experimental autoimmune uveoretinitis with poly (lactic acid) nanoparticles encapsulating betamethasone phosphate. *Exp Eye Res* 2006;82(4):657-663

57 de Kozak Y, Andrieux K, Villarroya H, Klein C, Thillaye-Goldenberg B, Naud MC, Garcia E, Couvreur P. Intraocular injection of tamoxifen-loaded nanoparticles: a new treatment of experimental autoimmune uveoretinitis. *Eur J Immunol* 2004;34(12):3702-3712

58 Sanders NN, Peeters L, Lentacker I, Demeester J, De Smedt SC. Wanted and unwanted properties of surface PEGylated nucleic acid nanoparticles in ocular gene transfer. *J Control Release* 2007;122(3):226-235

59 Janoria KG, Gunda S, Boddu SH, Mitra AK. Novel approaches to retinal drug delivery. *Expert Opin Drug Deliv* 2007;4(4):371-388

60 Kuno N, Fujii S. Biodegradable intraocular therapies for retinal disorders: progress to date. *Drugs Aging* 2010;27(2):117-134

61 Bakri SJ, Pulido JS, Mukherjee P, Marler RJ, Mukhopadhyay D. Absence of histologic retinal toxicity of intravitreal nanogold in a rabbit model. *Retina* 2008;28(1):147-149

62 Zhang G, Feng X, Wabner K, Fandrey C, Naqwi A, Wiedmann T, Olsen TW. Intraocular nanoparticle drug delivery: a pilot study using an aerosol during pars plana vitrectomy. *Invest Ophthalmol Vis Sci* 2007;48 (11): 5243-5249

63 Chen J, Patil S, Seal S, McGinnis JF. Rare earth nanoparticles prevent retinal degeneration induced by intracellular peroxides. *Nat Nanotechnol* 2006;1(2):142-150

64 Kuno N, Fujii S.Biodegradable intraocular therapies for retinal disorders: progress to date. *Drugs Aging* 2010;27(2):117-134

65 Schwartz SG, Flynn HW Jr.Fluocinolone acetonide implantable device for diabetic retinopathy. *Curr Pharm Biotechnol* 2011;12(3):347-351

66 Saraiya NV, Goldstein DA.Dexamethasone for ocular inflammation. *Expert Opin Pharmacother*2011;12(7):1127-1131

67 Koirala A, Makkia RS, Cooper MJ, Naash MI. Nanoparticle-mediated gene transfer specific to retinal pigment epithelial cells. *Biomaterials*2011; 32(35):9483-9493

68 Tamboli V, Mishra GP, Mitrat AK. Polymeric vectors for ocular gene delivery. *Ther Deliv*2011;2(4):523-536

69 Du J, Shi QS, Sun Y, Liu PF, Zhu MJ, Du LF, Duan YR. Enhanced delivery of monomethoxypoly (ethylene glycol)-poly (lactic-co-glycolic acid)-poly l-lysine NPs loading platelet-derived growth factor BB small interfering RNA by ultrasound and/or microbubbles to rat retinal pigment epithelium cells. *J Gene Med* 2011;13(6):312-323

70 Read SP, Cashman SM, Kumar-Singh R. A poly (ethylene) glycolylated peptide for ocular delivery compacts DNA into NPs for gene delivery to post-mitotic tissues *in vivo*. *J Gene Med* 2010;12(1):86-96

71 Hayashi A, Naseri A, Pennesi ME, de Juan E Jr. Subretinal delivery of immunoglobulin G with gold NPs in the rabbit eye. *Jpn J Ophthalmol*2009; 53(3):249-256

72 Mo Y, Barnett ME, Takemoto D, Davidson H, Kompella UB. Human serum albumin NPs for efficient delivery of Cu, Zn superoxide dismutase gene. *Mol Vis*2007;13:746-757

73 del Pozo-Rodríguez A, Delgado D, Solinís MA, Gascón AR, Pedraz JL. Solid lipid NPs for retinal gene therapy: transfection and intracellular trafficking in RPE cells. *Int J Pharm*2008;360(1-2):177-183

74 Farjo R, Skaggs J, Quiambao AB, Cooper MJ, Naash MI. Efficient non-viral ocular gene transfer with compacted DNA nanoparticles. *PLoS One*2006;1:e38

75 Liu HA, Liu YL, Ma ZZ, Wang JC, Zhang Q. A lipid nanoparticle system improves siRNA efficacy in RPE cells and a laser-induced murine CNV model. *Invest Ophthalmol Vis Sci*2011;52(7):4789-4794

76 Zhou X, Wong LL, Karakoti AS, Seal S, McGinnis JF. Nanoceria inhibit the development and promote the regression of pathologic retinal neovascularization in the Vldlr knockout mouse. *PLoS One* 2011;6 (2): e16733

77 Kong L, Cai X, Zhou X, Wong LL, Karakoti AS, Seal S, McGinnis JF. Nanoceria extend photoreceptor cell lifespan in tubby mice by modulation of apoptosis/survival signaling pathways. *Neurobiol Dis* 2011;42 (3): 514-523

78 Jin J, Zhou KK, Park K, Hu Y, Xu X, Zheng Z, Tyagi P, Kompella UB, Ma JX. Anti-inflammatory and antiangiogenic effects of nanoparticle-mediated delivery of a natural angiogenic inhibitor. *Invest Ophthalmol Vis Sci*2011;52(9):6230-6237

79 Park K, Chen Y, Hu Y, Mayo AS, Kompella UB, Longeras R, Ma JX. Nanoparticle-mediated expression of an angiogenic inhibitor ameliorates ischemia-induced retinal neovascularization and diabetes-induced retinal vascular leakage. *Diabetes* 2009;58(8):1902-1913

80 Kim JH, Kim MH, Jo DH, Yu YS, Lee TG, Kim JH. The inhibition of retinal neovascularization by gold NPs *via* suppression of VEGFR-2 activation. *Biomaterials*2011;32(7):1865-18671

81 Kalishwaralal K, Sheikpranbabu S, BarathManiKanth S, Haribalaganesh R, Ramkumarpandian S, Gurunathan S. Gold NPs inhibit vascular endothelial growth factor-induced angiogenesis and vascular permeability *via*Src dependent pathway in retinal endothelial cells. *Angiogenesis*2011; 14(1):29-45

82 Karthikeyan B, Kalishwaralal K, Sheikpranbabu S, Deepak V, Haribalaganesh R, Gurunathan S. Gold NPs downregulate VEGF-and IL-1 β -induced cell proliferation through Src kinase in retinal pigment epithelial cells. *Exp Eye Res*2010;91(5):769-778

83 Strettoi E, Gargini C, Novelli E, Sala G, Piano I, Gasco P, Ghidoni R. Inhibition of ceramide biosynthesis preserves photoreceptor structure and function in a mouse model of retinitis pigmentosa. *Proc Natl Acad Sci USA* 2010;107(43):18706-18711

84 Patel SR, Lin AS, Edelhauser HF, Prausnitz MR. Suprachoroidal drug delivery to the back of the eye using hollow microneedles. *Pharm Res*2011; 28(1):166-176

85 Kim JH, Kim JH, Kim KW, Kim MH, Yu YS. Intravenously administered gold NPs pass through the blood-retinal barrier depending on the particle size, and induce no retinal toxicity. *Nanotechnology* 2009;20 (50):505101

86 Kim H, Csaky KG. Nanoparticle-integrin antagonist C16Y peptide treatment of choroidal neovascularization in rats. *J Control Release* 2010; 142(2):286-293

87 Sakai T, Kuno N, Takamatsu F, Kimura E, Kohno H, Okano K, Kitahara K. Prolonged protective effect of basic fibroblast growth factor-impregnated NPs in royal college of surgeons rats. *Invest Ophthalmol Vis Sci*2007;48(7): 3381-3387

88 Ding XQ, Quiambao AB, Fitzgerald JB, Cooper MJ, Conley SM, Naash MI. Ocular delivery of compacted DNA-NPs does not elicit toxicity in the mouse retina. *PLoS One*2009;4(10):e7410

89 Wielgus AR, Zhao B, Chignell CF, Hu DN, Roberts JE. Phototoxicity and cytotoxicity of fullerol in human retinal pigment epithelial cells. *Toxicol Appl Pharmacol* 2010;242(1):79-90

90 Häfeli UO, Riffle JS, Harris-Shekhawat L, Carmichael-Baranauskas A, Mark F, Dailey JP, Bardenstein D. Cell uptake and *in vitro* toxicity of magnetic NPs suitable for drug delivery. *Mol Pharm*2009;6(5):1417-1428

91 Winkler DA, Mombelli E, Pietroiusti A, Tran L, Worth A, Fadeel B, McCall MJ. Applying quantitative structure-activity relationship approaches to nanotoxicology: Current status and future potential. *Toxicology*2012

92 Diebold Y, Calonge M.Applications of nanoparticles in ophthalmology. *Prog Retin Eye Res* 2010;29(6):596-609

93 Dombu CY, Betbeder D. Airway delivery of peptides and proteins using NPs. *Biomaterials*2013;34(2):516-525

94 Cordray MS, Amdahl M, Richards-Kortum RR. Gold nanoparticle aggregation for quantification of oligonucleotides: Optimization and increased dynamic range. *Anal Biochem*2012;431(2):99-105

95 Pannier AK, Segura T. Surface- and hydrogel-mediated delivery of nucleic Acid NPs. *Methods Mol Biol* 2013;948:149-169

96 Donaldson K, Schinwald A, Murphy F, Cho WS, Duffin R, Tran L, Poland C. The biologically effective dose in inhalation nanotoxicology. *Acc Chem Res* 2012

97 Arora M, Chan EK, Gupta S, Diwan AD. Polymethylmethacrylate bone cements and additives: A review of the literature. *World J Orthop* 2013;4 (2):67-74

98 Heidel JD, Schluep T. Cyclodextrin-containing polymers: versatile platforms of drug delivery materials. *J Drug Deliv*2012; 2012: 262731