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Review Article

Polymeric Matrices at Micro and Nanoscale for Ocular Drug Delivery

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Abstract: Drug delivery platforms have the potential to improve patient adherence, reduce side effects, increase efficacy for treatment of ocular diseases. Recent efforts in ocular drug delivery have been made to improve the bioavailability and precorneal residence through topical application. The potential use of polymeric micro and nanoparticles as drug carriers has led to the development of many advanced colloidal delivery vehicles. Drug loaded polymeric systems offer several favorable biological properties, such as biodegradability, nontoxicity, biocompatibility and mucoadhesive characteristics. These polymeric systems are amenable for targeted drug delivery, leading to decrease in dose, dosing frequency and thus lowering systemic toxicity. This review discusses the recent advances in polymeric micro and nanoparticles and their therapeutic significances in the field of ocular drug delivery.
Keywords: Drug delivery, ocular diseases, topical application, mucoadhesive.

INTRODUCTION

Polymeric microparticulate and nanoparticulate systems emerged as ocular drug delivery platforms since last few decades. New materials have been explored for encasing existing drugs which can enhance treatment by increasing bioavailability, decreasing toxicity, providing better tissue adherence, targeted delivery as well as increased duration of action. The challenges and requirements are different for the anterior and posterior ocular segments. However, the constraints are needed to be overcome for the treatment of the most prevalent posterior eye diseases. The design and development of novel topical delivery systems using polymeric gels, colloidal systems, and cyclodextrins has been shown to provide new therapeutic entities into the ocular milieu [1, 2]. It is established that typically, only 1% or less of a topically instilled dose was delivered into the anterior segments, and a negligible amount to the posterior segment [3, 4]. Currently, intravitreal injection is widely applied for posterior ocular delivery, but suffers from many drawbacks such as retinal detachment, cataract, endophthalmitis and increased intraocular pressure [5, 6]. Particle size ranges of microparticle drug delivery systems range from one micron to few mm approximately between 1-200 µm. Nanoparticle size ranges in nm, preferably less than a micron size. Microparticles could deliver macromolecules across various routes and tailor the release profile. Reports demonstrate that delivery of vaccines and molecules such as DNA for use in gene therapy could be carried out exploiting microparticles. Microparticles offers protection of the drug agent against chemical or physical degradation and improve stability. Microparticles can be administered periocular, by means of transscleral, sub-conjunctival, supra-choroidal application. Microparticles are fabricated from various natural and synthetic materials [8, 9]. The release rate can be tailored by modulating the molecular weight of the polymer, particle size and also by controlling polymeric framework nature. Polymers such as dextran and synthetic polymers like HPMA and poly (L-glutamic acid) are often used as drug carries. The microparticles can be embedded within a polymer or proteinic matrix network in either as solid aggregated state or a molecular dispersion, which will produce microspheres. Polyethylene and polystyrene microspheres are two mainly used polymers for microspheres. Microcapsules are containing core material is completely surrounded by a polymer shell. The shell is continuous, porous and sometimes non-porous polymeric type. Nanoparticles have been extensively applied for topical administration which significantly improved trans-epithelial characteristics of drugs [10, 12]. In some instances, nanoparticles appear to be promising platforms when compared to microparticulate systems depending upon the type and complexity and desired need of application.

MICRO PARTICULATE SYSTEMS

Micro particulate systems are exploited for wide range of application as drug delivery carriers,

including but not limited to vaccine delivery, oral delivery, transdermal delivery, ocular delivery. These particle size range of these colloidal drug carriers vary from one micron to few mm [13, 14]. These can be of two types namely microresorvoir and micro matrix. These monolithic spheres are dispersed in polymeric matrix at molecular level [15]. The techniques used for the preparation of these systems include solvent evaporation method [16], spray drying/emulsification techniques [17, 18]. Ionic interactions between ciprofloxacin (model drug) and the polyelectrolytes chondroitin sulfate or lambda carrageenan result in coprecipitates that can act as microparticulate controlled release systems, developed by Gavini et al. Chondroitin sulfate coprecipitates presented the superior particle size characteristics suitable for ocular application [19, 20]. Brimonidine-loaded microspheres were formulated using poly (lactic acid) (PLA) to release brimonidine at a constant rate for 35 days using transscleral delivery. New Zealand White rabbit eyes received a single administration of the microspheres and the intraocular pressure (IOP) reduced initially by 6 mm Hg and the effect was prolonged about a month [21, 22]. Microspheres of 5-fluorouracil (5-FU) with biodegradable polymers of lactic acid (PLA) or copolymers of polylactic-co-glycolic acid(PLGA). Poly (lactic acid) microspheres released 70-85% of total 5-FU over 7 days. The intravitreal kinetics of the microspheres were studied in ten rabbits *in vivo*. A suspension of microspheres was injected into the vitreous cavity of five normal eyes and five vitrectomized eyes. By 48 ± 5.2 days after injection, the microspheres disappeared from the vitreous cavity in the five normal eyes. Clearance from the vitreous cavity was accelerated in the five rabbits that underwent vitrectomy (14 ± 2.4 days; $P < 0.001$). This study suggests that microspheres as potential drug delivery systems to back of the eye. The controlled release drug delivery system for the long term inhibition of VEGF and its mediators. Poly (lactic -co- glycolic) acid(PLGA) microspheres loaded with anti- VEGF RNA aptamer (EYE 001), placed on the orbital surface of sclera and the release kinetics are investigated. PLGA microspheres are effective and able to sustain the drug release to posterior segments of eye with average rate of 2 µg/day over a period of 20 days [23]. Porous silicon was used for the delivery and sustained release of therapeutic molecules in various tissues by korhonen et al. The toxicity of porous silicon particles is concentration-dependent, and both positively and negatively charged porous silicon particles are well tolerated by human corneal and retinal epithelial cells [24, 25]. Gomes dos Santos *et al* designed PLGA microspheres for the sustained release of the nanosized anti-TGFβ2 (transforming growth factor β2) phosphorothioate antisense oligonucleotide complexes [26, 27]. Loftsson et al formulated water-soluble dexamethasone/γ-cyclodextrin (γCD) microparticles in a low-viscosity aqueous eye drop suspension. The aqueous suspension formulation was tested in rabbits (*in vivo*) and compared with an aqueous dexamethasone eye drop solution containing randomly methylated β-cyclodextrin (RMβCD). Two hours after single application of the dexamethasone/γCD eye drops to rabbits the concentration in vitreous was found to be 29 ± 16 ng/g, 86% of which reached vitreous via the topical route and in retina the concentration was 57 ± 22 ng/g (49% via topical route). For the RMβCD the values were 22.6 ± 9 and 66 ± 49 ng g^{-1} (73 and 14% via topical route), respectively. These steroid levels are comparable with the dexamethasone concentration achieved 1 month after intravitreal injection. The aqueous dexamethasone/γCD eye drop formulation was chemically stable during 7 months storage and well tolerated with no visible short-term side effects [28]. Efficient encapsulation of small hydrophilic/amphiphilic molecules into PLGA microspheres using novel emulsification technologies such as microfluidics, membrane emulsification and other techniques including spray drying and inkjet printing were discussed by Ramazani *et al* [29, 30]. Polyethylene glycol-polylactic acid (PEG–PLA) microparticles were developed by Rafat *et al* for encapsulation and delivery of a transactivator of transcription-enhanced green fluorescent protein fusion to retinal cells. PEG–PLA microparticles delivered proteins in cell culture allowing protein internalization with in 1 hour. *In vivo*, protein was shown to localize within the photoreceptor layer of the retina, and persist for at least 9 weeks with no observed toxicity [31].

NANO PARTICULATE SYSTEMS

The particle size of nanoparticle systems range between 50 nm -100 nm. There are wide range of techniques exploited used in the preparation of nanoparticles which include nano precipitation, nano encapsulation, super critical fluid technology, solvent evaporation, emulsification / solvent diffusion, homogenization method [32]. Bourges et al showed that an intravitreal injection of Poly lactide (PLA) nanoparticles resulted in trans-retinal movement, with a preferential localization in the retinal pigment epithelium (RPE). The presence of the nanoparticles within the RPE cells for 4 months after a single injection shows that a continuous and specific delivery of drugs can be achieved. Histology demonstrated anatomic integrity with no signs of toxicity [33]. Zhang et al reported that intravitreal injection of dexamethasone (DEX)-loaded poly (lactic acid-co-glycolic acid) nano particles sustained DEX concentrations for a long time in the posterior chambers thus can be used for the treatments of posterior segment diseases [34]. Nano particles prepared by using sialyl-Lewis X conjugated liposome as a site-directed delivery system containing dexamethasone showed selective targeting to the autoimmune uveo-retinitis [35]. Koirala et al reported that subretinal injections of rhodamine labeled nanoparticles using an RPE-specific reporter vector (VMD2-eGFP) can efficiently deliver genes to

the retinal pigmental epithelium and thus can be employed in the retinal gene therapy [36]. Albumin nanoparticles are an interesting delivery system for intravitreal drug administration that has shown controlled drug release and degradation to safe products. *In vivo* rat studies demonstrated their localization in the vitreous cavity and ciliary body for at least two weeks after a single intravitreal injection [37]. Delonix based fluorescent nanoparticles were prepared by a Quality-by-Design modified nanoprecipitation technique by Abayomi et al. Optimized nanoparticles had mean sizes < 240 nm, PDI < 0.2 and zeta potential of < −30 mV. Mixture of surfactants with different HLB values controlled nanoparticle swelling. Nanoparticles, stable in the presence of simulated lachrymal fluid and lysozyme, sustained the drug release. *In vitro* studies indicated that nanoparticles in concentration range of 100–1483.3 μg/mL on retinal and corneal epithelial cells. Flow cytometry and confocal microscopy techniques showed that retinal cells did uptake 18% of the nanoparticles but not corneal cells [38]. Photoresponsive *in situ* forming injectable implants are still in the early stages of development with limited reports on their safety and effectiveness. Advantages include ease of application in a minimally invasive manner and site specific tailored drug release. Moreover, the biodegradable implants avoids the need for surgical intervention. Incorporating polymeric nanoparticles into these implants may reduce the high initial burst release from the polymeric matrix and further sustain drug release, avoiding frequent injections [39]. Nanoparticles fabricated from the biodegradable and biocompatible polymer, polylactic-co-glycolic acid (PLGA) were developed by Salama *et al*. The spherical nanoparticles exhibited biphasic release profile and the drug was entrapped amorphous in the nanoparticles. Optimized nanoparticles, injected subconjunctivally in normotensive Albino rabbits, were able to reduce the IOP for up to 10 days at lower particle size when compared to large particles. Topical surface-modified PLGA nanoparticles were developed to improve the drug delivery efficiency to the retina. Chitosan, glycol chitosan and polysorbate 80 was used as surface modifiers. Coumarin-6 was used as a model drug and fluorescent marker, and after ocular administration of PLGA nanoparticle eye drops, the fluorescence intensity of coumarin-6 was observed in the retina. Delivery to the mouse retinal layers after topical administration was increased by surface modification with different agents used in the study [40]. Nanoparticle was developed to target choroidal neovascularization (CNV) via topical ocular administration by Chu et al. The resulting particle size was 67.0±1.7 nm, and the zeta potential of the particles was −6.63±0.43 mV. Dual-modified nanoparticles displayed significant targeting and penetration ability both *in vitro and in vivo*, indicating that it is a promising drug delivery system for managing CNV via topical ocular administration [41]. Chen *et al* developed hyaluronic acid coated human serum albumin nanoparticles. They were administered into the eye cups and continuous US with a frequency of 1 MHz, an intensity of 0.5 W/cm^2, and a duration of 30 s was applied once or repeatedly via the transscleral route. Short pulses of US significantly improved the diffusive mobility of NPs through the vitreous as well as their penetration across the neural retina into the retinal pigment epithelium and choroid without causing any detectable damage to the ocular tissues [42].

CONCLUSION

Nanotechnology based delivery systems possess great potential to resolve the shortcomings of existing strategies for drug delivery to the ocular posterior segment. The micro and nanoparticulate systems appears to be promising in terms of biocompatibility, biodegradability, higher precorneal residence and enhanced ocular bioavailability. Topical administration of drugs still needs to be addressed with viable alternative optimized formulations owing to concentrations obtained in the eye. The data presented in this review hold promise for new delivery systems in dosing drugs to the ocular posterior segment. Recent advancements in nanotherapies for retinal diseases using a range of platforms have also shown promising results. Considering both pros and cons of nanoparticulate systems, it is expected that better treatment approaches emerge for retinal diseases in the future.

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