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Therapeutic Significance of Polymeric Nano Particles as Carriers for Sustained Ocular Therapy: An Overview.

Santhi Kumaraswamy*, Sokalingam Arumugam Dhanaraj, Sridevi Chigurupati, and Selvadurai Muralidharan.

Unit of Pharmaceutical technology, Faculty of pharmacy, AIMST University, Semeling, 08100, Kedah state, Malaysia.

ABSTRACT

Effective delivery of drug to the eye poses many problems through conventional eye drops due to its poor ocular retention and bioavailability. The use of nanocarriers provides interesting opportunities for topical ocular drug delivery. The association of an active drug to nanocarriers allows the drug to closely interact with specific ocular structures, also to overcome ocular barriers and to prolong its residence in the target area. Hence delivery of a drug through nanoparticles can accomplish main benefits like enhancement of drug permeation, controlled release, and targeting. Though several non polymeric and colloidal drug delivery systems, such as Prodrugs, Polymeric micelles, liposomes, neosome, nanoemulsions, nanocrystals and nanoparticles have been largely investigated and reported to enhance ocular bioavailability of ocular drugs. Owing to the submicron size of polymeric nanoparticles they are well tolerated and have the tendency to deposit in the cul-de-sac for prolonged period. In the present review our objective is focused on the fundamental aspects of polymeric nanoparticles as carrier for ocular drugs and its therapeutic applications with special emphasis to research studies in ocular delivery of polymeric nanoparticles with anti- infectious and anti inflammatory drugs.

Keywords: Ocular, Polymeric nanoparticles, fundamentals, anti infectious drugs and anti-inflammatory drugs.

Corresponding author

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INTRODUCTION

Polymeric nanoparticles are defined as particles with a diameter of less than 1µm.They are made up of either biodegradable materials or non biodegradable polymers from synthetic or natural source. Drugs can be either integrated in the matrix or attached to the surface. Nanoparticles made up of various biodegradable polymers like polylactides (PLAs), polycyanoacrylate, poly (D, L-lactides), natural polymers like chitosan, gelatin, sodium alginate and albumin can be used effectively for efficient drug delivery to the ocular tissues. The topical application of any drug to the eyes in conventional solution leads to lachrymal drainage and subsequent drug loss [1]. The main reason for this is due to tear turn over and tear dilution. The ocular bioavailability of most of the drugs is drastically reduced due to this hitch. There is a need for an appropriate delivery system which could increase the contact time of the drug with the eye surface and facilitate the transport of drug molecules into the eye tissue. Some of the novel carriers such as polymeric nano particles have several advantages over the conventional systems by increasing their efficacy and reducing the toxicity. Polymeric nanocarriers are designed to release drug for a prolonged period of time, thereby enhances its absorption [2]. Several other nano carriers like liposomes, noisome and nano emulsions, were also reported to be useful in enhancing ocular bioavailability of many drugs, but the physicochemical properties of these carries, such as particle size, surface properties, and composition, were found to influence the fate of both the drug and the carrier significantly [3]. The physicochemical characteristics are critical for the nanoparticles, for their adhesion to corneal mucosa.

Diseases of the eye vary from minor conjunctivitis to irreversible visual impairment caused mainly by diseases of the posterior eye. The most prevalent posterior eye diseases which cause visual impairment include age-related macular degeneration (AMD), macular edema secondary to retinal vein occlusion, uveitis, diabetic retinopathy, cytomegalovirus (CMV) retinitis and retinitis pigmentosa [4]. Drug administration to inner ocular tissues and posterior segments of the eye such as the retina, choroids, and the vitreous body is a significant challenge. The most serious limitations of ocular drug therapy are with eye diseases of the posterior segment [5, 6] because drugs applied to the surface of the eye often fail to reach the back of the eye. The overall aim of developing nanoparticles for ocular delivery is to improve the ocular bioavailability with eventual reduction in dose.

The rationale behind the development of a carrier for ocular drugs

The necessity of using a carrier for ocular drugs is the key is to achieve adequate bioavailability by longer ocular residence. There are many challenges for ocular drug delivery systems. In some cases, the goal is to stop or reverse problems such as degenerations in the retina and neovascularisation in the cornea and in the retina. In other cases, the drugs must contribute to the success of refractive corneal surgery and the healing process, tissue transplantation and growth factor delivery for retinal and corneal regenerative medicine, and gene therapy for hereditary retinal disorders [7]. The main reasons for the low bioavailability of ocular drugs are due to the biopharmaceutical problems related to the special characteristic of the eye that restricts drug. The eye is partially isolated from the remainder of the body by several types of barriers like corneal epithelium, and muco-aqueous layer of tear film that impede the effective passage of many drugs leading to a minimal absorption[8]. Based on the aforementioned points it is considered to be important to develop an effective carrier like polymeric nano particulate system for ocular therapy.

Distinctive benefits of polymeric nanoparticles as carriers for ocular delivery

Nanoparticles encapsulated drug will have better stability, and due to its increase in half –life, the frequency of administration of drug will also be reduced. The Nanoparticulate loaded drug would be devoid of plasma peak concentration, resulting in decreased toxicity. The localization of drug in RPE cells (retinal pigment epithelium) or corneal mucous membrane may prolong the drug residence time, which subsequently produces reduction in total dose. By accomplishing the dose reduction, the dose related systemic side effects could be minimized with improved patient compliance. The main disadvantage of using polymeric nanoparticulate system is the risk associated with type of system which is in the form of injections and vitreous clouding [9].

Types of polymers used in the preparation of nanoparticles for ocular therapy

For the preparation of nanoparticles various types of synthetic, natural and copolymers could be used. The following list [10] comprised of polymers which have been commonly studied in ocular based nanoparticles.

Synthetic Polymers

It includes Poly- lactides (PLA), Poly – (lactide-co-glycolide) (PLGA), Poly epsilon-caprolactone (PECL), Eudragit, and Poly lactide-co-glycolide-Poly ethylene glycol (PCL-PEG) Poly butyl cyano acrylate (PBCA).

Natural polymers

It includes Alginate, Gelatin and Albumin and Chitosan.

Common Methods of preparation of polymeric nanoparticles for ocular therapy and their principles

Even though in-numerous type of newer methods of preparation of nanoparticles have been introduced and reported recently [11 and 12, 13]. In our review we are limiting our focus on the principle underlying in methods which are most widely used in ocular based nanoparticles.

Supercritical fluid technicque

In this method the solute of interest is solubilized in a supercritical fluid which is environmental friendly unlike other toxic solvents, and the solution is expanded through a nozzle. Thus, the solvent power of super- critical fluid dramatically decreases and the solute eventually precipitates. This technique is clean because the precipitated solute is completely solvent free. Unfortunately, most polymers exhibit little or no solubility in supercritical fluids, thus making the technique less of practical interest. This technicque was very popular in the late 80s and early 90s for particle production of bioerodible drug-loaded polymers like PLA [13].

Emulsification–solvent evaporation method

This is the oldest method of preparation of nanoparticles developed from a preformed polymer. This method was originally proposed by Gurney et al [14] they applied biodegradable polymers to produce drug carriers. In this method, emulsions are formulated with polymer solutions prepared in volatile solvents. Conversion of the emulsion into a nanoparticle suspension occurs by the evaporation of the polymer solvent which is allowed to diffuse through the continuous phase of the emulsion [10, 15, 16] this is a slow process performed under vacuum.

Emulsification–solvent diffusion/emulsification solvent displacement method

This method shows good reproducibility. The polymer solvent used to prepare the emulsion needs to be partly soluble in water [10, 17] then, the emulsion is prepared with water saturated with the polymer solvent composing the oil phase, and with an oil phase saturated with water as continuous phase. Mutual saturation of both polymer solvent and water is obtained by mixing the two liquids in equal volume and waiting for phase separation to collect the solvent saturated water at the bottom and water saturated organic solvent at the top of the resulting two phase system.

Ionic gelation method

This method is applicable to the nano particles produced from natural polymers a like alginate and chitosan. Nanoparticles obtained from ionic gelation procedure are synthesized in totally aqueous media. They are included among the few organic solvent free methods. Ionic nano gels can be obtained from aqueous solutions of charged polysaccharides, which gel in the presence of small ions of opposite charges. The gelation of the polysaccharide should be performed in very dilute solution using concentrations of the gelling agent below the gel point. This corresponds to the pre-gel phase in which the chains of the polymer reacting with the gelling agent are forming small clusters that can be high lighted by electron microscopy or by a clear reduction

of the viscosity of the polysaccharide solution. Clusters formed in the pre-gel phase are stabilized by forming complex with opposite charged polyelectrolytes [10,18].

The emulsification–reverse salting out method

The emulsification–reverse salting out method is very close to the emulsification–solvent diffusion method. The main difference arises from the composition of the emulsion. The emulsion is formulated with a polymer solvent which is normally totally miscible with water, i.e. acetone the artifact used to emulsify the polymer solution in the aqueous phase consists in dissolving high concentration of salt or sucrose chosen for their strong salting out effect in the aqueous phase. Examples of suitable electrolytes are magnesium chloride, calcium chloride, and magnesium acetate [10] these components retain the water molecules for their own solubilization; hence modify the miscibility properties of water with other solvents such as acetone.

The precipitation of the polymer dissolved in the droplets of the emulsion can be induced through a reverse salting out effect which is simply obtained by dilution of the emulsion with a large excess of water [10, 19].

Gelation of the Emulsion Droplet

The nanoparticles form by cooling down the emulsion resulting in the gelation of the emulsion droplets. With other polymers like alginate and pectin, gels form by adding a second component or by modifying the pH of the polymer solution. In this case, two different emulsions will be prepared, one containing the gelling polymer in the dispersed phase and the other containing the gelling agent or the pH controlling agent in the dispersed phase [10, 20, 21,]. The two emulsions will be mixed together under strong agitation to enhance collisions between droplets which are required to induce the gelation of the polymer, hence formation of nanoparticles.

Indispensable barriers for drug delivery in ocular therapy

Drug delivery to anterior segment of eye

Cornea of the eye is considered to be the effective barrier for delivery of any foreign molecule. The ocular bioavailability in the anterior segment of eye could be enhanced by prolonging the drug residence in cornea and also by enhancing corneal penetration. But the bioavailability of an instilled conventional drug onto the ocular surface is usually low. Considerable amount is lost due to physiological mechanisms, such as tear drainage and blinking, after instillation. Thus, there are a short pre-corneal residence time, usually less than two minutes and a non productive absorption thorough the well vascularised conjunctiva and the nasolachrymal drainage system.

Presently, the major problem is due to the limited absorption of drug, and limited access to intraocular tissues through the conjunctival pathway, and the risk of systemic side effects.

For those reasons, intensive research in recent decades has focused on increasing the corneal penetration of topically applied drugs through nanospheres. These delivery systems have been considered to offer the possibility of a more simplistic delivery and transport across tissues, and consequently their potential has been investigated and proven in many cases [22]. Hence a prolonged local drug delivery could be achieved using nanospheres. The surface characteristics of the nanocarriers can influence the interaction with the ocular surface structures. Nanoparticles due to their biocompatibility, biodegradability, and mucoadhesive ness, transiently enhances the permeability of mucosal barriers. [23]

Drug delivery to posterior segment of eye

Transcorneal penetration of topically administered ophthalmic medicines into the posterior segment is frequently required for certain treatments such as infectious or noninfectious intra ocular inflammation, in such conditions the drugs are given into the vitreous. The vitreous is a gelatinous, cell-free structure that is capable of retaining molecules and also delivering them to nearby structures. Frequent intraocular injections

are needed to treat retinal disorders. These injections produce undesired side effects, like increased risk of cataract development, vitreous hemorrhage, retinal detachment, and endophthalmitis.

Hence to avoid frequent intravitreal injections to treat serious intraocular disorders, serious efforts have been put to use carriers like nanospheres.

Even though the cornea constitutes one of the most selective barriers to foreign molecules for the eye, transcorneal penetration of topically administered ophthalmic medicines for the posterior segment is a major concern. Hence recently the drug delivery devices like nanospheres have been studied a lot for intraocular diseases eventually this may reduce the frequency of intravitreal injections and also improve the intraocular bioavailability [24, 25], The idea of using nanoparticles for delivery of drugs to the posterior segment is by retaining the molecules in vitreous cavity where the nanoparticles can release drug in a slow manner, with eventual drug release for loner time [26]. There are promising studies reported in the recent literature on the use of intravitreal injected NPs. Ganciclovir-loaded albumin NPs are an interesting example. For single intravitreal injections in rats, these nanospheres were reported to be safe, well-tolerated for Ganciclovir. These nanoparticles were found to be present in the vitreous and ciliary body for at least two weeks. [27].

Nanoparticles as potential carrier in anti - infectious and anti -inflammatory ocular therapy

Polymeric nanoparticles in ocular inflammation

The most common disease affecting the eye is inflammation. Topical therapy with corticosteroids is quite common in the treatment of ocular inflammatory disorders but their use is often associated with severe side effects such as increase in intraocular pressure, cataract formation and risk of infection. Non-steroidal anti-inflammatory drugs (NSAIDs) like Indomethacin, flurbioprofen, ketorolac and diclofenac which are devoid of these side effects have been found to be safer alternatives to steroids in treating ocular inflammation [26].

Eudragit RL 100-based aceclofenac nanoparticles were prepared by nanoprecipitation [28] Rajesh Katara et.al have studied the drug loading efficiency with different drug to polymer ratio. It was reported that a drug–polymer ratio of 1:10 showed the highest entrapment efficiency. It has been found that the particles showed low poly dispersity index, and positive zeta potential. The positive zeta potential and fine particle size would help to prolong the corneal contact time. The nanoparticle was found to provide a biphasic release pattern with an initial burst release followed by sustained release. It had a best fitting into Higuchi-square-root release kinetics. Transcorneal permeation studies through excised goat cornea indicated about 2-fold increase in permeation of drug from nanosuspension formulation compared with an aqueous solution of aceclofenac of same concentration.

In vivo ocular anti-inflammatory study indicated that the lid closure was prominent up to 3 hr after which, it decreased. The eyes, which were treated with aceclofenac nano formulation, showed smaller lid closure scores as compared to their respective controls. The nano formulation also showed higher anti-inflammatory activity compared to that of aqueous solution of drug. They concluded that the eudragit nanoparticle of aceclofenac were effective in reducing dose frequency and improving patient compliance for ocular delivery.

Naproxen–eudragit RS100 nanoparticles were formulated by Khosro Adibkia et.al [29] by applying single emulsion–solvent evaporation/extraction process, it was reported that all nanoparticles displayed a slowed release pattern with the reduced burst release in comparison with the intact drug powder and physical mixtures of drug and polymer.

Polymeric Nanoparticles in ocular fungal infections

Amphotericin-B is a polyene antifungal antibiotic that has broad-spectrum activity. It remains the drug of choice for systemic fungal infection as well as various serious ocular infections like fungal keratitis.

A study conducted by Swarnali Das et.al [30] indicated the potential of Eudragit RL nanospheres for the specific delivery of antifungal drug Amphotericin-B to the ocular mucosa. These systems showed great

promise with regard to the particle size and zeta potential. Particle size was further confirmed by TEM studies. They also reported that the drug loading did not affect the native charge of the polymer and the Eudragit has not lost its positive surface charge and it also maintained the similar kind of particle size in blank as well as drug-loaded nanospheres. This charge could facilitate an effective adhesion to the corneal surface and account for a strong interaction with the negatively charged mucosa of the conjunctiva and anionic mucin present in the tear film, prolonging the residence time of the formulation.

In vivo eye irritation study was carried out by Draize eye irritation test. It has been found that there was no irritation with nanoparticle treated animals. All the irritation study data showed that the values of irritation and opaqueness were almost zero. They confirmed that the prepared Eudragit RL nanospheres containing Amphotericin -B was suitable for treating fungal infections in ocular cavity.

Studies conducted by Monika Yadavet.al [31] have reported on the formulation of novel polymer-surfactant nanoparticle formulation using the anionic surfactant di-octyl sodium sulfo succinate and polysaccharide polymer gum cordia, for prolonging the contact time of Fluconazole. The optimized formulation of Fluconazole-loaded gum cordial nanoparticles was compared with the commercial formulation of Fluconazole eye drops for their corneal permeation characteristics using an isolated goat cornea mounted over modified Franz-diffusion cell. They have observed that there was no significant difference between the %cumulative permeation of Fluconazole from the nanosuspension formulation, in comparison to commercial aqueous formulation. Even though the test formulation was in suspension form, it provided permeation comparable to solution dosage form, which may be attributed to nanometric size of suspended particles.

Polymeric nanoparticles in ocular bacterial infections

An investigation done by Himanshu Gupta et.al [32] reveals the preparation of PLGA nanoparticles of Sparfloxacin using a modified nanoprecipitation technique. They have tried different drug-to-polymer ratios to obtain low particle size with maximum encapsulation efficiency. A particle size below 250 nm with a polydispersity index near 0.25 was considered optimum for ocular administration. All formulations under that study showed zeta potential of –22 mV.

In vivo precorneal drainage of the developed formulation was assessed by gamma scintigraphy. For scintigraphic studies, Sparfloxacin was radio labeled with radionuclide Tc-99m. After administration of the radio labeled formulation, a good spreading was observed over the entire precorneal area. The marketed formulation cleared very rapidly from the corneal region and reached into the systemic circulation via the naso lacrimal drainage system as significant activity was recorded in kidney and bladder after 6 hours of ocular administration, whereas PLGA nanosuspension formulation was retained at the corneal surface for longer duration as no significant radioactivity was observed in the systemic circulation.

Ocular irritation of the developed formulation was checked by hen's egg chorioallantoic membrane test, which is a rapid, sensitive, and inexpensive test. The developed formulation was tested by using this method, and it was found to be non irritant. It has been concluded that, the developed PLGA-Sparfloxacin nanosuspension yielded appropriate particle size, extended release, with better tolerability, and prolonged retention at the corneal site.

Another study done by Sabetha et.al [33] revealed the formulation of chitosan nanoparticles containing Moxifloxacin. They have concluded that the formulated moxifloxacin nanoparticles of chitosan as a carrier was found to be suitable and potential natural carrier in terms of their particle size, zeta potential, drug loading capacity, *in vitro* release characteristics and better ocular tolerability. The release profile of Moxifloxacin from nanoparticles has shown a sustained character. The overall results demonstrated the effective use of moxifloxacin loaded chitosan nanoparticles as a controlled release preparation for treatment of ocular conjunctivitis infection.

Polymeric nanoparticles as viral vector in ocular gene therapy

The potential for gene delivery to the eye using adeno-associated virus (AAV) vectors has received much recent attention. There are two main approaches by which therapeutic AAV-mediated gene transfer might be useful in the context of ocular disease. First, AAV- mediated gene therapy has the potential to correct

the specific gene defect in conditions, where the defect is well understood. Correction of an ocular genetic defect requires gene delivery directly to the defective cells and has been successfully used to slow photoreceptor loss in several rodent models of primary photoreceptor disease [34].

The field of viral gene therapy in the retina has developed various successes. Example of a successful viral gene therapy treatment comes from a phase I clinical trial using AAV (adeno-associated viral vector) to deliver pigment epithelium-derived factor (PEDF) to the eyes of patients diagnosed with age-related macular degeneration (AMD) and showed a significant level of reduction in neo angiogenesis associated with disease progression. Modified HIV vectors have been used to preserve some retinal function in two recessive retinitis pigmentosa models. Nanoparticles also have great potential as a strategy for gene therapy and can be used to treat genetic defects *in vitro and in vivo*.

A study done by Konstan et.al [35] revealed that the compacted-DNA nanoparticle mediated gene therapy provides a safe, effective and promising system for the delivery of therapeutic genes to target tissues in the eye. They drive very specific and high levels of gene expression and the expression can be sustained for several months. The safe use of compacted DNA nanoparticles in the clinical setting reveals their viability as a potential treatment strategy for human condition. The use of this system in the treatment of genetic diseases of the eye promises to be a strong alternative to the existing collection of viral vectors. [36]

CONCLUSION

Ocular drug delivery system based on polymeric nanoparticles has been proven to be an effective carrier, for sustaining drug delivery of many pharmaceuticals in the current research surge. However to be more viable from the clinical prospective, these polymeric nanoparticles need to be developed with an narrow size range, optimum drug loading for both hydrophilic and lipophilic drugs, low ocular irritation, biocompatibility, and lack of toxicity. In future it is worth while to investigate many conventional ocular suspensions through nanoparticulate drug delivery technology.

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