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Nanotechnology in ocular drug delivery

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Despite numerous scientific efforts, efficient ocular drug delivery remains a challenge for pharmaceutical scientists. Most ocular diseases are treated by topical drug application in the form of solutions, suspensions and ointment. These conventional dosage forms suffer from the problems of poor ocular bioavailability, because of various anatomical and pathophysiological barriers prevailing in the eye. This review provides an insight into the various constraints associated with ocular drug delivery, summarizes recent findings and applications of various nanoparticulate systems like microemulsions, nanosuspensions, nanoparticles, liposomes, niosomes, dendrimers and cyclodextrins in the field of ocular drug delivery and also depicts how the various upcoming of nanotechnology like nanodiagnostics, nanoimaging and nanomedicine can be utilized to explore the frontiers of ocular drug delivery and therapy.

Nanotechnology, a term derived from the Greek word nano, meaning dwarf, applies the principles of engineering, electronics, physical and material science and manufacturing at a molecular or submicron level. Materials at the nanoscale could be a device or a system or, alternatively, supramolecular structures, complexes or composites. An early promoter of nanotechnology, Albert Franks, defined it as that area of science and technology where dimensions and tolerances are in the range of 0.1–100 nm [1]. In addition to the developments in other scientific disciplines, such as electronics and robotics, nanotechnology is expected to make significant advances in mainstream biomedical applications, including the areas of gene therapy, drug delivery, imaging and novel drug discovery techniques. Increasing use of nanotechnology by the pharmaceutical and biotechnology industries is widely anticipated. The global market for medical nanotechnology is expected to be more than $3 billion within five years.

Nanotechnology in drug delivery

The development of effective drug delivery systems that can transport and deliver a drug precisely and safely to its site of action is becoming a highly important research area for pharmaceutical researchers. Indeed, a great number of new delivery technologies surface each year and nearly every part of the body has been studied as a potential route for administrating both classical and novel medicines. Consequently, promising ways of delivering poorly soluble drugs, peptides and proteins have been devised. In addition, attractive drug delivery technologies, such as transdermal patches, nanodevices, bioadhesive systems, implants, micro fabricated systems, cell encapsulation devices and novel nasal drug delivery systems are currently under intensive study [1–4]. Although there are many potential improvements to be made in the fields of drug delivery and diagnostics, nanotechnology offers advantages that allow a more targeted drug delivery and controllable release of the therapeutic compound [2,5]. The aim of targeted drug delivery and controlled release is to manage better drug pharmacokinetics, pharmacodynamics, non-specific toxicity, immunogenicity and biorecognition of systems in the quest for improved efficacy.

Nanotechnology and ophthalmology

Ocular drug delivery is one of the most interesting and challenging endeavors faced by the pharmaceutical scientist, because of the critical and pharmacokinetically specific environment that exists in the eye [6–9]. The anatomy, physiology and biochemistry of the

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eye render this organ exquisitely impervious to foreign substances [10,11]. In the eye, the inner and outer blood–retinal barriers separate the retina and the vitreous from the systemic circulation and the vitreous body and reduces convection of molecules since it has no cellular components [12].

Considering these points, the development of a drug delivery system (DDS) is becoming increasingly important in the treatment of vitreoretinal diseases, not only to facilitate drug efficacy, but also to attenuate adverse effects [13]. In ocular diseases, where angiogenesis is a feature, such as choroidal neovascularisation (CNV), diabetic retinopathy, central retinal vein occlusion and intraocular solid tumors, drug targeting can be an efficient mode of treatment. Since the retina has a specific environment with no lymph system, retinal neovascularization and CNV are supposed to have an environment similar to solid tumors, having enhanced permeability and retention (EPR) effects and are suitable for drug targeting [12]. Ocular drug targeting has three major goals:

- Enhancing drug permeation (e.g. iontophoresis and transscleral DDS);
- To control the release of drugs (e.g. micro spheres, liposomes, and intraocular implants);
- To target drugs (e.g. prodrugs with high molecular weight and immunoconjugates).

Significance of nanotechnology in ocular drug delivery

Even though the various drug delivery systems mentioned above offer numerous advantages over conventional drug therapy, nonetheless, they are not devoid of pitfalls, including

- Poor patient compliance and difficulty of insertion for ocular inserts.
- Tissue irritation and damage caused by penetration enhancers and collagen shields.

Much of the published data suggests that in the case of ophthalmic drug delivery, an appropriate particle size and a narrow size range, ensuring low irritation, adequate bioavailability and compatibility with ocular tissues, should be sought for every suspended drug [14]. Other formulation factors, that is the use of correct wetting, suspending and buffering agents, protective colloids, preservatives, and so on, should also be carefully considered. Thus, an optimum ocular drug delivery system should be one which can be delivered in the form of eye drops, causing no blurred vision or irritability and would need no more than one to two administrations per day [15]. Various criteria that need to be considered, while deciding the formulation parameters for developing a suitable ophthalmic drug delivery system are shown in (Table 1). Though the delivery of drugs to the anterior segment of the eye is achieved mainly through topical delivery, very little of the topically applied drug reaches the posterior segment of the eye. This necessitates the administration of some drugs, such as anti-glaucoma drugs, corticosteroids and certain antibiotics by the systemic route. However, a very small fraction of the dose reaches the ocular tissues, following systemic administration. The doses required to give a therapeutic effect via this route, however, can lead to considerable side effects.

The use of nanotechnology-based drug delivery systems like nanosuspensions, solid lipid nanoparticles and liposomes has led to the solution of various solubility-related problems of poorly soluble drugs, like dexamethasone, budenoside, gancyclovir and so on [16]. Drugs can also be targeted to mononuclear phagocyte systems to allow regional specific delivery and minimize side effects in other organs [17]. Besides this, depending on their particle charge, surface properties and relative hydrophobicity, nanoparticles can be designed to be successfully used in overcoming retinal barriers. In addition to these points, encapsulation of drugs in nanospheres, liposomes, and so on, can also provide protection for the drug and hence prolong exposure of the drug by controlled release [16]. Nanotechnology-based drug delivery is also very efficient in crossing membrane barriers, such as the blood retinal barrier in the eye [18,19]. The drug delivery systems based on nanotechnology may prove to be the best drug delivery tools for some chronic ocular diseases, in which frequent drug administration is necessary, for example in ophthalmic diseases like chronic cytomegalovirus retinitis (CMV). In this disease, the topical delivery of drugs like ganciclovir (GCV) is prevented and intravitreal delivery is preferred. Though the half-life of GCV, following intravitreal administration, is 13 h, frequent injections are necessary to maintain therapeutic levels, since this drug prevents the replication of the viral deoxy ribononucleic acid (DNA), but does not eliminate the virus from the tissue. Therefore, long term therapy is necessary, which may result in cataract development, retinal detachment and endophthalmitis [20] GCV intravitreal implants can be used, which release drugs for six to eight months, but there can be issues, such as side effects like astigmatism and vitreous hemorrhage; moreover, the need for surgery to remove the implants seriously restricts their use [21–27]. These difficulties can be overcome by using nanoparticles made up of various natural polymers like albumin, because of their smaller size and controlled release properties. When delivered to the eye, these nanoparticles did not induce inflammatory reactions in the retinal tissue or disturb the organization of the surrounding ocular tissues

TABLE 1

Criteria for the selection of optimal formulation parameters when developing an ophthalmic drug delivery system

Factor	Preference
Drug	Preferentially lipophilic. Non-ionisable lipophilic compounds will concentrate into the corneal epithelium, while ionisable lipophilic ones will partitionate into the aqueous humor
Vector type	Depends on encapsulated molecule. Should allow a high loading dose to reduce the instilled volume
Carrier size	Lowest as possible to facilitate corneal uptake and passage
Osmotic pressure	Isotonic with physiological fluids to avoid irritation and lacrimation
pH	Close to physiological pH to avoid irritation and lacrimation. If buffering is necessary, the lowest possible buffer concentration is to be used (<0.1 M)

[28]. Nanotechnology-based drug delivery is also suitable in the case of the retina, as it has no lymph system, hence retinal neovascularization and CNV have similar environments to that of solid tumors, in which the EPR effect may be available for drug targeting by nanoparticles [12]. The major problem of intravitreal injection is of inducing the stimulation of pathogenic immune responses, resulting in photoreceptor degeneration [29–36]. Various studies have also shown that intravitreal administration of nanoparticles did not generate organ-specific autoimmune phenomena.

Different nanoparticulate-based drug delivery systems

The development of various nanoparticulate-based drug delivery systems, like nanoparticles, nanoemulsions, nanosuspensions, liposomes, dendrimers, niosomes, Cyclodextrins and so on, can enhance the rate of ophthalmic drug delivery to a significant degree (Figure 1).

Microemulsions

Microemulsions were first described by Hoar and Schulman [37] and are dispersions of water and oil that require surfactant and co-surfactant agents in order to stabilize the interfacial area. They have a transparent appearance, thermodynamic stability and a small droplet size in the dispersed phase (<1.0 μm).

Microemulsions are an interesting alternative to topical ocular drug delivery, because of their intrinsic properties and specific structures; they can be easily prepared through emulsification, can be easily sterilized, are stabile and have a high capacity for dissolving drugs [38]. The administration of oil-in-water microemulsions could be advantageous, because the presence of surfactant and co-surfactant increases membrane permeability, thereby increasing drug uptake. In this case, these systems act as penetration enhancers to facilitate corneal drug delivery [39]. The surfactant and co-surfactant molecules will facilitate the passage of drug through the corneal membrane.

Moreover, microemulsions achieve sustained release of a drug applied to the cornea and higher penetration into the deeper layers of the ocular structure and the aqueous humor than the native drug. These systems offer additional advantages including: low viscosity, a greater ability as drug delivery vehicles and increased properties as absorption promoters. Furthermore, the possibility of prolonged release of drugs in microemulsions makes these vehicles

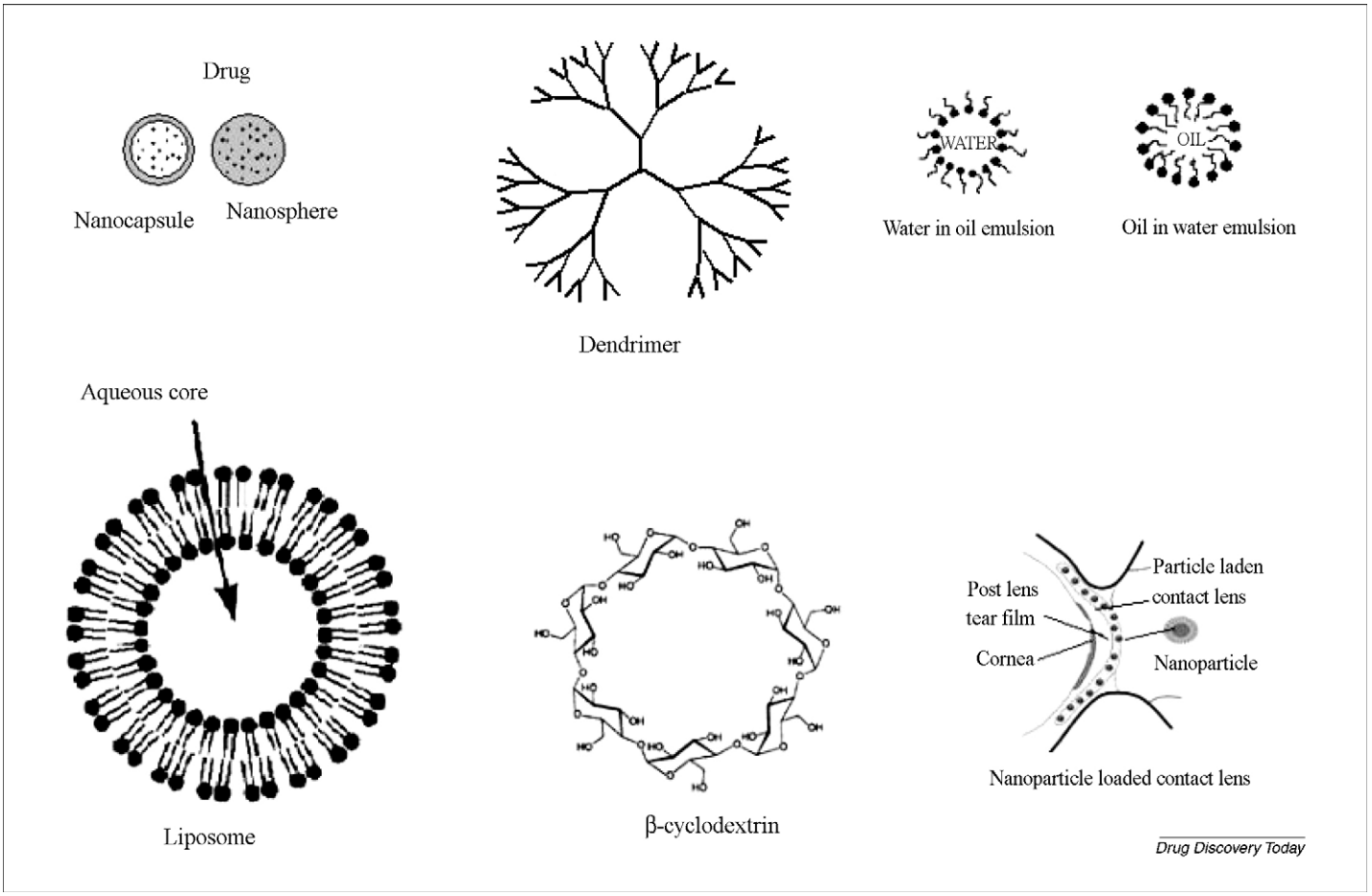

FIGURE 1

A schematic representation of different, nanoparticulate-based, ophthalmic drug delivery systems. Nanoparticles are small polymeric colloidal particles with a therapeutic agent either dispersed in the polymer matrix (nanosphere) or encapsulated in polymer (nanocapsule). Dendrimers are mono dispersed symmetric macromolecules built around a small molecule with an internal cavity surrounded by a large number of reactive end groups. Microemulsions are dispersions of water and oil with surfactant and co surfactant in order to stabilize the interfacial area. Liposomes are small artificial vesicles of spherical shape that can be produced from natural phospholipids and cholesterol. They can encapsulate drugs inside the cavity or between the bilayers depending on the hydrophilicity or the hydrophobicity of the drug. CDs are a group of cyclic oligosaccharides, capable of forming inclusion complexes with many drugs. Drugs once encapsulated in the nanoparticulate systems can also be loaded in the contact lenses to increase their ocular bioavailability.

very attractive for ocular administration and can greatly decrease the frequency of application of eye drops [38]. There are many formulations of microemulsions intended for ophthalmic use. Studies have also shown that some pilocarpine-based microemulsions delay the activity of the drug in such a way that twice daily instillations of these systems were equivalent to four instillations of conventional eye drops [40]. Besides this, the low surface tension of microemulsions also guarantees a good spreading effect on the cornea and mixing with the precorneal film constituents, thus possibly improving the contact between the drug and the corneal epithelium [37]. Some of the developed microemulsions also presented a viscosity value that allows sterile filtration and easy dispensing as eye drops.

Nanosuspensions

Nanosuspensions consist of pure, poorly water-soluble drugs, suspended in an appropriate dispersion medium. Nanosuspension technology can be better utilized for drug compounds that form crystals with high energy content, which renders them insoluble in either organic (lipophilic) or hydrophilic media [16].

Polymeric nanoparticle suspensions, which are prepared from inert polymeric resins, can be utilized as important drug delivery vehicles, capable of prolonging drug release and enhancing bioavailability. Since these carriers do not irritate cornea, iris or conjunctiva, they act as an inert carrier for ophthalmic drugs. Flurbiprofen (FLU) loaded in polymeric nanoparticle suspensions, prepared from Eudragit RS 100® and RL 100® polymer resins; are reported to prevent myosis induced during extracapsular cataract surgery. FLU is a non-steroidal anti-inflammatory drug (NSAID) that inhibits cyclooxygenase and, thus, antagonizes papillary constriction during intra-ocular surgery. It also reduces the infiltration of polymorpho nuclear leukocytes (PMNs) in the aqueous humor and, thus, significantly decreases post-surgical oedema following intra-ocular surgery. Since the FLU-loaded nanosuspensions are prepared by the quasi-emulsion solvent diffusion (QESD) technique, which generally avoids the toxic chemicals used in solvent evaporation techniques, they have great potential for ophthalmic application [41,42]. The positive charge on the nanoparticle surface facilitates their adhesion to the corneal surface [43]. Thus, it can be accepted that the use of nanosuspensions in ophthalmic pharmaceutical formulations is an attractive area, offering a great possibility to overcome the inherent difficulties associated with ocular drug delivery.

Nanoparticles

Nanoparticles are defined as particles with a diameter of less than 1 μm, consisting of various biodegradable materials, such as natural or synthetic polymers, lipids, phospholipids and even metals. 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, gelatine, sodium alginate and albumin can be used effectively for efficient drug delivery to the ocular tissues.

Nanoparticulate drug delivery has demonstrated promising results in ophthalmic drug delivery over the last 10 years. Studies conducted by Bourges *et al.* in rabbits has shown that nanoparticles of different size and electric charge, when injected into the vitreous, migrate through the retinal layers and tend to accumulate in the retinal pigment epithelium (RPE) cells. They also observed the presence of nanoparticles within the RPE cells up to four months after a single intravitreous injection [44]. This movement of nanoparticles has taken place because of rupture of the internal limiting membrane (ILM) because of the modification of the vitreous interface structure secondary to the presence of the PLA and poly (D,L-lactide-co-glycolide) (PLGA). The inflammatory reactions following the injection may also have contributed to the ease of transretinal movement of the nanoparticles into the vitreous cavity and rapid settling on the ILM. Intravitreous injection may induce non-specific activation of the retinal microglial cells and a mild transient inflammation can modify the. permeability and anchoring mechanism of the ILM. These findings can be clinically implemented to design novel drug delivery systems targeting the posterior segment of the eye in general, and to the RPE cells and retina in particular. The bioavailability of drugs also increases when encapsulated in such nanospheres. Recently, it has been reported that non-biodegradable polystyrene nanospheres (<2 μm) can be observed within the neuroretina and RPE, 2 months after a single intravenous injection in rabbits [45]. Moreover, nanoparticles act at the cellular level and can be endocytosed/phagocytosed by cells, with the resulting cell internalization of the encapsulated drug. In the case of nanoparticles, both the surface charge and the binding of the drug to the particles were found to be more important than the drug loading. Li *et al.* [46] showed that, though being fully (100%) encapsulated in polybutyl cyano-acrilate nanospheres, the drug progesterone did not get released properly, because of strong interaction between the drug and the polymer.

Studies have shown that albumin nanoparticles can serve as a very efficient drug delivery system for ophthalmic diseases, like CMV retinitis, as they are biodegradable, non-toxic and have non-antigenic properties. Since they have high content of charged amino acids, albumin nanoparticles allow the adsorption of positively charged GCV or negatively charged particles like oligonucleotides [28]. Moreover, nanoparticles made up of other natural polymers, like chitosan, are also effective in intraocular penetration of some specific drugs, because of their ability to contact intimately with corneal and conjunctival surfaces. In addition, nanoparticles can also be coated with different polymers to improve adhesion. Studies have shown that the bioavailability of encapsulated indomethacin doubled when Poly(epsilon-caprolacton) (PECL) nanoparticles were coated with chitosan [47]. Greater corneal penetration was also obtained, when PECL nanoparticles were coated with polyethylene glycol (PEG) [48]. All these studies lead us to believe that nanoparticles have great potential as drug delivery systems for ocular tissues.

Liposomes

Liposomes are small artificial vesicles that can be produced from natural non-toxic phospholipids and cholesterol. Because of their size, amphiphilic properties and biocompatibility, liposomes are promising systems for drug delivery. Liposome properties vary substantially with lipid composition, size, surface charge and the method of preparation. The behavior of liposomes as an ocular drug delivery system has been observed to be, in part, because of their surface charge. Positively charged liposomes seem to be preferentially captured at the negatively charged corneal surface,

compared with neutral or negatively charged liposomes. According to Felt *et al.* [49] cationic vehicles are expected to slow down drug elimination by lacrymal flow by increasing the viscosity of the solution and by interacting with the negative charges of the mucus. The binding affinity of liposomes to the cornea suggests that that liposome uptake by the cornea is greatest for positively charged liposomes, less for negatively charged liposomes and least for neutral liposomes, suggesting that the initial interaction between the corneal surface and liposomes is electrostatic in nature. Positively charged unilamellar liposomes enhance transcorneal flux of penicillin G across isolated rabbit cornea more than four-fold [50]. The findings suggest that liposomes enhance corneal penetration of drug by being adsorbed onto the corneal surface, with direct transfer of drug from liposomal to epithelial cell membranes.

Similarly, immunoliposomes of antiviral drugs, like GCV and iododeoxyuridine, using monoclonal antibodies to glycoprotein D of herpes simplex virus, have also been reported [51]. It was reported that these site-specific and sustained release immunoliposomes could act as improved vehicles for drug delivery in treatment of ocular Herpes simplex virus infection. Antisense oligonucleotides that can be efficiently used to treat ocular diseases like CMV retinitis can be encapsulated in the liposomes and efficiently targeted to retina [52]. Studies conducted by Bochot *et al.* [65] showed the retention of 37% of the administered oligonucleotides in the vitreous humor even after 15 days. It has been also shown that administration of liposome encapsulated phosphodiester (16-mer oligothymidylate) (pdT16) oligonucleotides resulted in sustained release into the vitreous and retina-choroid, compared with the release from the solution and in a reduced distribution to the non-targeted tissues (sclera, lens) [52]. In addition, liposomes also helped to protect phosphodiester oligonucleotides against degradation. Despite the above discussed factors, which make liposomes a potentially useful system for ocular delivery, they are not very popular because of their short shelf life, limited drug capacity, use of aggressive conditions for preparation and problems in sterilization.

Niosomes

Niosomes are non-ionic surfactant vesicles and, like liposomes, are bilayered structures, which can entrap both hydrophilic and lipophilic drugs. Niosomes in topical ocular delivery are preferred over other vesicular systems because: they are chemically stable, compared to liposomes; can entrap both lipophilic and hydrophilic drugs; have low toxicity because of their non-ionic nature; unlike phosholipids, handling of surfactants does not require special precautions and conditions; they exhibit flexibility in their structural characterization, for example in their composition, fluidity, and size; can improve the performance of the drug via better availability and controlled delivery at a particular site; they are biodegradable, biocompatible, and non-immunogenic [53]. Non-ionic surfactant vesicles have been reported successfully, as ocular vehicles for cyclopentolate. In the *in vivo* study, niosomes, independent of their pH, significantly improved the ocular bioavailability of cyclopentolate, with respect to reference buffer solution, indicating that it can be used as an efficient vehicle for ocular drug delivery [50]. A modified form of niosomes, the discomes, are also used in ophthalmic drug delivery systems. Discomes are large structures (12–16 μm) derived from niosomes by the addition of non-ionic surfactant, that is Solulan C24. They have particular advantages for ocular drug delivery, since, as a result of their larger size, they can prevent their drainage into the systemic pool; also their disc shape could provide a better fit in the cul-de-sac of the eye [50,54]. Discomes are prepared by the progressive incorporation of Solulan C24 into the vesicular dispersion that leads to the partitioning of this soluble surfactant into the lipid bilayer until a critical level is reached. This results in the formation of a large flattened disc-like structure (discomes) in place of the spherical structures [50]. The studies carried out by Vyas *et al.* showed that the entrapment efficiency of timolol maleate (water soluble drug) is higher in discomes than niosomes [55]. Moreover, an increase in ocular bioavailability was observed when timolol maleate was entrapped in niosomes and discomes compared with maleate solution.

Dendrimers

Dendrimers are macromolecular compounds made up of a series of branches around an inner core. They are attractive systems for drug delivery because of their nanometer size range, ease of preparation and functionalization, and their ability to display multiple copies of surface groups for biological recognition processes [56–58]. Because of these properties, they can be used as an effective vehicle for ophthalmic drug delivery. Robinson *et al.* [59] suggested the use of bioadhesive polymers, such as poly (acrylic) acids, to improve drug delivery and release by optimizing contact with the absorbing area in order to prolong residence time and decrease dosage frequency. These bioadhesive polymers, however, are associated with problems like blurred vision and formation of a veil in the corneal area, leading to loss of eyesight. To avoid these problems, dendrimers like poly(amidoamine) (PAMAM) are used, which are liquid or semi-solid polymers and have several amine, carboxylic and hydroxyl surface groups, which increases with the generation number (G0, G1, G2, and so on). Because of this unique architecture, PAMAM dendrimers, are able to solubilize strongly and poorly water-soluble drugs into their inner zones containing cascading tiers of branch cells with radial connectivity to the initiator core and an exterior or surface region of terminal moieties [60–62]. So, greater possibilities can be explored by using dendrimers as ophthalmic drug delivery vehicles.

Cyclodextrins

Cyclodextrins (CDs) are a group of cyclic oligosaccharides capable of forming inclusion complexes with many drugs [63]. Through CD complexation, the aqueous solubility of some hydrophobic drugs can be enhanced without changing their molecular structure and their intrinsic abilities to permeate biological membranes. In ophthalmic preparations, co-administration of CDs has been reported to increase corneal penetration, ocular absorption and the efficacy of poorly water-soluble drugs such as dexamethasone, cyclosporin, acetazolamide, and so on. It is seen that CDs act as true carriers by keeping hydrophobic drug molecules in solution and delivering them to the surface of the corneal epithelium where they partition. CDs increase aqueous stability and bioavailability of ophthalmic drugs [63–65]. Freedman *et al.* [66] reported a significantly increased bioavailability for pilocarpine (1 μg/μl) in

a 5% 2-hydroxypropyl- β-cyclodextrin (HP-β-CD) solution compared to pilocarpine alone. Similarly, Usayapant *et al.* [67] also reported that HP-β-CD increases the ophthalmic bioavailability of dexamethasone and dexamethasone acetate. Unlike conventional penetration enhancers such as benzalkonium chloride, which disrupt the biological barrier, the increase in bioavailability of drugs by CDs is because of their interaction with biological membranes. CDs are very effective in decreasing drug irritation because, by forming inclusion complexes, they mask the irritating effects of the drugs. Although pilocarpine prodrugs cause severe eye irritation, studies have shown that pilocarpine prodrug/sulfobutylbutylether β-cyclodextrin (SBE 7-β-CD) complexes act as a depot that limits free prodrug concentration at the precorneal area to a non-irritating level [68]. It is seen that a very small fraction of the applied CDs penetrates into the cornea, conjunctiva, sclera or other tissues at the eye surface, which is harmless. In rabbits, aqueous eye drop solutions containing as high as 45% of the more hydrophobic HP-β-CD have been found to be non-irritating. Similar results have been seen in humans and other animals [69]. Various nanoparticulate drug delivery systems used in ophthalmic research are listed in (Table 2).

Nanoparticle-loaded contact lenses

The use of contact lenses loaded with nanoparticles can be an effective alternative to topical application of ophthalmic drugs in the form of eye drops. It has been observed that, in the presence of a lens, drug molecules will have a much longer residence time in the post lens tear film, compared with about 2–5 min in the case of topical application of drugs in the form of eye drops [15,70]. This longer residence time enhances drug permeation through the cornea and minimizes drug absorption into the blood stream through the conjunctiva or nasolacrymal duct. Drug loaded contact lenses can also provide continuous drug release, because of slow diffusion of the drug molecules through the particles and the lens matrix. The soaked contact lenses also delivered drugs only for a period of a few hours for some typical drugs. The soaked contact lenses also suffer from major limitations like, the amount of drug that can be loaded in the lens matrix by this approach depends on the equilibrium solubility of the drug in the lens matrix, which is small for most drugs. The other limitation is that drugs loaded by soaking also diffuse in few hours. Hence, contact lenses soaked in drug solution cannot be used for long-term drug delivery.

The duration of drug delivery from contact lenses can be significantly increased if the drug is first entrapped in vesicles, such as liposomes, or nanoparticles, such as microemulsions. Such nanoparticles can then be dispersed throughout the contact lens material. The entrapment of drug in nanoparticles also prevents the interaction of drug with the polymerization mixture. This provides additional resistance to drug release, as the drug must first diffuse through the nanoparticle and penetrate the particle surface to reach the hydrogel matrix. Gulsen *et al.* conducted experiments to study the dispersion of drug loaded oil-in-water (o/w) microemulsions in poly-2-hydroxyethyl methacrylate (p-HEMA) hydrogels. Their studies showed that the drug residence time was enhanced significantly and there were two separate time scales for the drug release: an initial burst releasing 50% of the drug in the first few hours and then a slower release over a few days. The initial release was because of the release of drug adsorbed on the surface of the nanoparticles and the gel, the long-term release was because of the release of the drugs trapped inside the oil drops. The drug

TABLE 2

Nanoparticulate drug delivery systems used in ophthalmic research

S. no	Drug	Nanoparticulate system	Result	Refs
1	Oligonucleotides	Liposomes	Better control of release rate	[73]
2	Acetazolamide	Liposomes	Produced a marked decrease in intra ocular pressure (IOP)	[74]
3	Pilocarpine HCl	Liposomes	Increased miotic response and ocular bioavailability of the drug	[75]
4	Inulin	Liposomes	Increased ocular concentration of the drug	[76]
5	Cyclopentolate	Niosomes	Promoted ocular absorption of the drug	[77]
6	Timolol maleate	Discomes	Entrapped comparatively higher amount of drug than niosomes	[55]
7	GCV	Albumin nanoparticles	Increased antiviral activity against human cytomegalovirus (HCMV) infection	[28]
8	Pilocarpine	Microemulsions	Decreased IOP by 25%	[78]
9	Amikacin	Nanoparticles	Improved delivery of drug to cornea and aqueous humor	[79]
10	Pilocarpine	Poly(butyl)-cyano acrylate nanoparticles	Enhanced miotic response by 22% and decreased IOP	[80]
11	Flurbiprofen	Acrylate polymer nanosuspensions	Obtained higher drug levels in the aqueous humor and inhibition of Paracentesis-induced miosis	[41]
12	Cyclosporin	Chitosan nanoparticles	Enhanced delivery to external ocular tissues	[81]
13	Rhodamine	PEG and chitosan coated PECL nanoparticles	Obtained better corneal penetration	[48]
14	Dexamethasone	Microemulsions	Enhanced bioavailability in aqueous humor	[37]
15	Pilocarpine nitrate, Tropicamide	Dendrimers	Prolonged miotic activity	[82]
16	Pilocarpine nitrate	HP-β-CD	Increased miotic enhanced corneal penetration effect and by four-fold	[64]
17	Dexamethasone	HP-β-CD	Enhanced solubility, permeability, and corneal bioavailability	[83,84]

release rates from contact lenses in the eyes are seen to be different from those in a well-stirred beaker. For eyes, a fraction of the released drugs gets lost through tear drainage and adsorption through the conjunctiva; though the majority of the drug loaded in the lens is released in the post lens tear film. Here, the drug has a residence time of 30 min and are absorbed into the cornea. But a fraction of the drug is also released into the prelens tear film and is lost. The loss of drugs by this route is not very significant, as the prelens tear film breaks up in approximately 1–3 s because of frequent blinking of eye [71,72].

Future perspectives

There are likely to be multiple applications of nanotechnology in ophthalmology. Nanotechnology can help in making nanodevices for complex eye surgeries, like glaucoma, retinal vascular surgery and so on, and also in the development of new lens material for cataract treatment. It will also benefit the different delivery formats: injectable, oral, implantable, transscleral, and so on. Moreover, the development of different nanotechnology-based tools can be used for improving imaging, screening and research techniques, including nanolithography, nanoarrays and mass spectrometry, which can be used in the field of discovery of ophthalmic drugs. Nanotechnology formulations can also be used for resolving solubility issues and increasing the number of compounds available for potential development. Beside this, nanotechnology can also help to develop an effective and robust DNA nanoparticle therapy for the treatment of genetically based blinding diseases. It can even help in generation of scaffolds for tissue bioengineering, especially for neural stem cells and also use of these for the delivery of growth factors and the stem cells.

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