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Nanotechnological approaches in Ophthalmic delivery systems

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Abstract

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, ointment and other drug delivery devices like inserts, implants, gelling systems, etc. These conventional and novel dosage forms suffer from the problems of poor ocular bioavailability, because of various anatomical and patho physiological 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 nanosuspensions, nanoparticles, dendrimers, etc. and depicts how the various upcoming of nanotechnological approaches will be utilized to explore the frontiers of ocular drug delivery and therapy for the prolongation of residence time of the device to reduce the repeated instillation.

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INTRODUCTION

Nanotechnology – a term derived from the Greek word "nano" meaning dwarf – is the engineering of functional system at molecular or submicron scale. In the quest for improving efficacy nanotechnology offers advantage that allows a more targeted drug delivery and controllable release of therapeutic

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compound with the aim to manage better drug pharmacokinetics, pharmacodynamic, nonspecific toxicity, immunogenity and biorecognition of system. Nanotechnology –based drug delivery systems, depending on their particle charge, surface properties and relative hydrophobicity, can be designed to be successfully used in overcoming retinal barriers and providing protection for the encapsulated drug, prolonging exposure by controlled release. It also has led to solution of various solubility-related problems of poorly soluble drugs and can be used to target mononuclear phagocyte system to allow region-specific delivery and minimize side effect in other organs[1]

Drug delivery system based on nanotechnology with an appropriate particle size and narrow size range, ensuring low irritation, adequate bioavailability and compatibility with ocular tissues, may prove to be being the best delivery tools for pharmaceuticals treating ocular diseases, and such a system should be investigated for every suspended drug[2].

Materials at the nano scale could be a device or a system or, alternatively, supra molecular structure or a complex or composite. An early promoter of nanotechnology, Albert franks defined it as area of science and technology where dimensions and tolerance are in the range of 0.1 -100nm. In addition to development 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[3].

Challenges in Ophthalmic drug delivery systems

Ocular drug delivery is one of the most interesting and challenging endeavors facing pharmaceutical scientists. The anatomy, physiology, and biochemistry of the eye provide a unique structure that restricts the entry of drug molecules at the required site of action. A suitable ocular formulation should release the drug overcoming the protective barriers of the eye without causing permanent tissue damage. For anterior-segment drug delivery, common routes of administration are topical instillation and sub-conjunctival injection, whereas for posterior segment drug delivery common routes include systemic dosing, periocular and intravitreal injections, and topical dosing[4].

Topical ocular administration of drugs has two different purposes: to treat superficial eye diseases, such as infections (e.g., conjunctivitis, blepharitis, keratitis sicca), and to provide intraocular treatment through the cornea for diseases such as glaucoma or uveitis. For their favorable cost advantage, the greater simplicity of formulation development and production, and the good patient acceptability, more than 90% of the marketed ophthalmic formulations are in the form of eye drops; yet these conventional systems cannot be considered optimal in the treatment of vision-threatening ocular diseases, as most of the drugs are washed from the eye by various mechanisms (lacrimation, tear dilution, and tear turnover). Moreover, the relatively impermeable corneal barrier restricts the entry of foreign substances. As a result, less than 5% of administered drug penetrates the cornea and reaches intraocular tissues.

The cornea consists of three membranes: epithelium, endothelium, and inner stroma. The corneal epithelium, lipophilic in nature, acts as a selective barrier for small molecules and prevents the diffusion of macromolecules via the paracellular route. The stroma, located below the epithelium, is a highly hydrophilic layer making up 90% of the cornea.[5]

The corneal endothelium consists of a single layer of flattened epithelium like cells and is responsible for maintaining normal corneal hydration. Because the cornea is characterized by lipophilic and hydrophilic structures, it represents an effective barrier to the

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absorption of both hydrophilic and lipophilic molecules.[6]

After instillation of an ophthalmic drug solution, the drug is first mixed with the lacrimal fluid and remains in contact with the ocular mucosa for a very short period of time, typically 1–2 minutes, because of the continuous production of lacrimal fluid (0.5–2.2 μL/min). Drainage through the upper and lower Canaliculus into the lacrimal sac, which opens in the nasolacrimal duct, induces a rapid elimination of conventional dosage forms during blinking. The conjunctiva and sclera are more permeable than the cornea for drugs topically applied into the eye, but the circulation removes the drugs before it can be absorbed by inner ocular tissues. Both transconjunctival penetration and transnasal absorption after drainage are generally undesirable, not only because of the loss of active ingredient but also because of possible severe systemic side effects. Drugs penetrate across the corneal epithelium via the transcellular pathway (mainly for lipophilic drugs) or para cellular pathway. The transcorneal penetration seems to be hindered by the binding of the drug to the corneal tissues, so that these tissues seem to act as drug reservoirs.[7]

In the case of ionizable drugs (weak acids and weak bases), their permeation depends on the chemical equilibrium between the ionized and non- ionized forms in the eye drop and eventually in the lacrimal Fluid. It is well known that the lipid membranes are more permeable to the non-ionized form of the drug than the ionized form. Besides the degree of ionization, another relevant issue affecting the corneal penetration is the charge of the ionized molecule. Hydrophilic charged cationic compounds permeate more easily through the cornea than anionic forms, because the corneal epithelium is negatively charged above its isoelectric point.[8] Also, the pH and buffering capacity of the instilled solution can have a significant effect on ophthalmic drug absorption.

To overcome the disadvantages of eye drops, several ophthalmic drug delivery systems have been investigated, which can control the release of the drug and sustain therapeutic levels over an extended period of time. The efforts have been concentrated on the development of formulations that maximize ocular drug absorption through prolongation of the drug residence time in the cornea and conjunctival sac, as well as enhancing precorneal drug penetration and decreasing the drug release time from the delivery system.[9]

Nanomedicines for ocular therapy

Substantial efforts have been directed toward the development of ocular drug delivery systems that would prolong the drug retention, allowing the drug to remain in contact with the cornea for longer duration and thus increasing bioavailability. Nanoparticulate technology is advocated as an ophthalmic drug delivery approach that may enhance dosage form acceptability while providing sustained release in the ocular milieu. Particle size, particle size distribution, and stability constitute a major issue considered by formulation scientists when formulating dispersed systems, especially those intended for parenteral or ocular administration. Very small particles such as nanoparticles are well tolerated and possess adhesive properties, which could prolong the residence time of the drug in the cul-de-sac, prevent tear washout (due to tear dynamics), and increase ocular bioavailability.

Other potential advantages of nano-scaled drug delivery systems in ocular therapy are[10]:-

(1) The possibility of self-administration by patients as eye drops.

(2) No impairment of sight because of small dimensions of the delivery systems.

(3) Protection against metabolic enzymes (such as peptidases and nucleases).

(4) Possible uptake into corneal cells.

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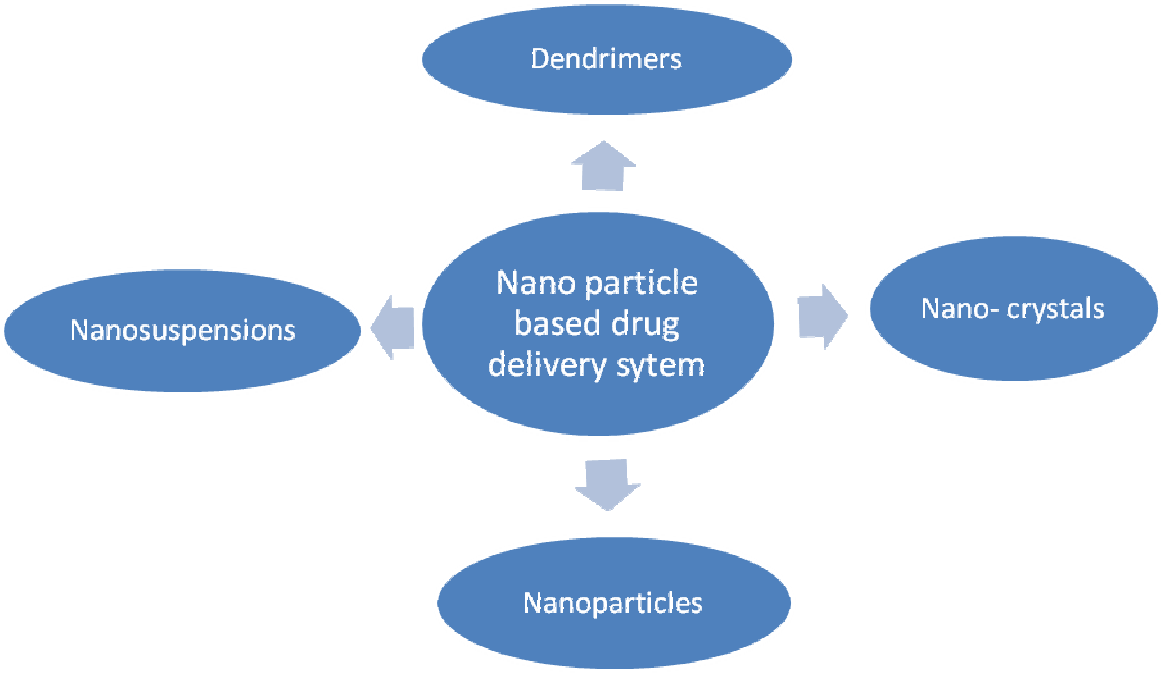
(5) Prolonged drug release, reducing the need for repeated instillation or injection; and

(6) Targeting toward affected tissues, reducing possible side effects and required dose.

Approaches in nanoparticulate-based drug delivery systems



Therapeutic Significance of Nanotechnology-based in Ocular Drug Delivery

A colloidal carrier system may be applied in liquid form like eye drop solutions, where upon their interaction with the glycoprotein of the cornea and conjunctiva can form a precorneal depot resulting in prolonged release of the bound drug. Nanotechnology-based drug delivery is also very efficient in crossing membrane barriers, such as the blood-retinal barrier in the eye and can function as excellent systems for chronic ocular diseases requiring frequent drug administration, like chronic cytomegalovirus retinitis (CMV).

Nanoparticles

Nanoparticles are defined as particles with a diameter of less than 1 mm, 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 polylactide (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.[29]

Nanoparticulates differ from macroscopic objects because of sub-micron properties such as high surface area and energy, and movement of the particles in liquid media (Brownian motion). Size, morphology and physical state of the encapsulated drug as well as molecular weight and crystallinity of the polymer influence drug release and degradation of the nanoparticles. Surface charge of nanoparticles determines the performance of the nanoparticle system in the body, e.g. interactions with cell membranes. Zeta (ζ) potential measurements provide information about the particle surface charge.[11]

Particle size of externally applied colloidal carriers influences absorption or permeation through the

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ocular barriers. Drug loading efficiency of particles is dependent on size and shape of carriers.

Uptake of PLGA particles in rabbit conjunctival epithelial cells was found to be dependent on the particle size. Smaller (100-nm) particles exhibited the highest uptake compared to larger (800-nm and 1000 nm) particles and particles of 100 nm were able to penetrate across the corneal barrier. Delivery of drugs to the posterior site of eye by application of drug solution is very difficult. The possibility of DNPs i.e. drug loaded nano-particles to reach the posterior site of ocular tissues and deliver drugs at targeted sites at effective therapeutic concentration in various disorders like age related macular degeneration, retinitis, diabetic retinopathy, and corneal/conjunctival squamous cell carcinoma is very high.[12]

Calvo et al, observed a similar size-dependency pattern with the in-vivo corneal uptake of indomethacin-loaded poly (epsiloncaprolactone) colloidal particles. The observed uptake was higher than micro particles after topical application on the albino rabbit eye. The size dependency and efficiency of uptake along with the facilitated uptake of bovine serum albumin indicated that PLGA nanoparticles can be used for enhancement of ocular drug absorption and the controlled release of proteins and drugs. [13]

Surface modification or coating by biocompatible (hydrophilic) polymers like PEG, poloxamer and poloxamines improve the uptake of nanoparticles and enhance stability. The presence of PEG on the surface of nanospheres can modulate the interfacial properties of the carrier, thereby, can positively influence the mucoadhesion and improved drug permeation.

Fresta et al, investigated the effect of coating the surface of acyclovir-loaded polyalkyl-2-cyanoacrylate nanospheres with PEG moieties by a simple adsorption process. [14] Giannavola et al, studied the effect of PEG coating on PLA nano-sphere and reported that coated nanospheres were much more efficient in improving the ocular bioavailability of acyclovir.[15] Lopez-Leon et al, reported that chitosan particles undergo volume phase transitions (swelling/shrinking processes) upon alteration of the physicochemical conditions of the medium. Alteration of pH from acidic to basic values caused a de-swelling process[16].

Nanoparticle suspensions, prepared from Eudragit RS 100 and RL 100 are reported to prevent myosis induced during extracapsular cataract surgery. Bucolo et al, have investigated the ocular pharmacodynamic profile of nanoparticles loaded with sodium ibuprofen (IBU-RS) and compared with administration of an aqueous solution of ibuprofen lysinate (IBL) in the rabbit eye. The IBU-RS nano-suspension formulation significantly reduced the primary signs of ocular inflammation protein level and the number of polymorphonuclear leukocytes in the aqueous Humor compared with the IBL formulation. Additionally, the nanocapsules produced a lower degree of cardiovascular effect in comparison to aqueous eye drops because of reduced non-corneal absorption.

The in-vivo studies of nanoparticles of piroxicam:Eudragit RS100 formulated using the solvent evaporation/extraction technique, and of methylprednisolone acetate (MPA) formulated by using a copolymer of poly(ethylacrylate, methyl-methacrylate and chloro trimethyl ammonio ethyl methacrylate) revealed that inflammation was inhibited by the DNP suspension more significantly than the microsuspension of drug alone in the rabbit eye with endotoxin-induced uveitis.

For increased retention in the precorneal pocket, the hydrolipophilic properties of the polymer-drug system of DNPs need to be optimized. Li et al, studied poly butyl cyanoacrylate nanoparticles loaded with [^{3}H] progesterone using a hydrophilic continuous phase. Tissue concentration of progesterone following topical administration of

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nanoparticles was generally four to five times less than that observed with control solutions, due to the high affinity of progesterone as the drug becomes less available for absorption during its residence time in the precorneal area. [17]

Polymeric nanocapsules of metipranolol for ocular delivery was developed using polyisobutylcyanoacrylate (PIBCA) and polyepsiloncaprolactone (PECL) and evaluated for the ability of this colloidal system to prevent the conjunctival absorption of metipranolol and subsequent systemic side effects. The formation (PIBCA) or precipitation (PECL) of the polymer around the oily nanodroplets prevents their coalescence during the solvent evaporation process. Consequently, the final particle Size is smaller than the droplet size of the control emulsion. The influence of the oil is explainable in terms of its hydrophobic character: the more hydrophilic oil (Labrafil) is dispersed to a greater extent, and hence, a smaller particle size was obtained. It was concluded that the polymeric coating formed around the oily droplets is not a continuous polymeric wall. Hence, the nature of the oil should be considered as the main factor determining the particle surface charge of the nanocapsules.[18]

Studies conducted by Bourges et al, in a rabbit has shown that nanoparticles 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. [30]

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. It has been reported that non-biodegradable polystyrene nanospheres (<2 mm) can be observed within the neuroretina and RPE, 2 months after a single intravenous injection in rabbits. [19]

Moreover, nanoparticles act at the cellular level and can be endocytosis/ 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, 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.[21]

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 nonantigenic 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[22]. 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

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of encapsulated indomethacin doubled when Poly (epsilon-caprolactone) (PECL) nanoparticles were coated with chitosan[23] .Greater corneal penetration was also obtained, when PECL nanoparticles were coated with polyethylene glycol (PEG). All these studies lead us to believe that nanoparticles have great potential as drug delivery systems for ocular tissues.[24]

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 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.[25]

Flurbiprofen (FLU) loaded in polymeric nanoparticle suspensions, prepared from Eudragit RS 1001 and RL 1001 polymer resins are reported to prevent myosis induced during extra capsular cataract surgery. FLU is a non-steroidal anti-inflammatory drug (NSAID) that inhibits cyclo oxygenase and, thus, antagonizes papillary constriction during intra-ocular surgery. It also reduces the infiltration of polymorphonuclear 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 .The positive charge on the nanoparticle surface facilitates their adhesion to the corneal surface.[26] 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.[27]

It could be shown that the nano-particles possess a prolonged retention time in the eye, most likely due to their adhesive properties. From this poorly soluble drug could be administered as a nano-suspension. The development of such a colloidal delivery system for opthalamic use aims at droppable dosage form with a high drug loading and a long lasting drug action. The nano-suspensions were prepared by a modification of the quasi-emulsion solvent diffusion technique using variable formulation parameters. Nano suspensions had a mean size around 100nm and a positive charge, this make them suitable for ophthalmic applications. In-vitro dissolution test indicated a controlled release profile of IBU for nanoparticles. In vivo efficacy was assessed on the rabbit eye after induction of an ocular trauma. An inhibition of the mitotic response to the surgical trauma was achieved, comparable to control aqueous eye drop formulation, even though a low concentration of free drug in conjunctival sac was reached from the nanoparticle system. Drug level in aqueous humour was also higher after application of the nanosuspensions; moreover, IBU- loaded nanosuspensions did not show toxicity on ocular tissues.[28]

Nano-crystals

By definition, drug nano-crystals are nanoparticles, being composed of 100% drug without any matrix material, typically with a size range between 200 and 500 nm. Several methods are used to reduce the particle size of a drug—that is, bottom-up and top-down technologies.[29]

The bottom-up technologies begin by dissolving the molecules and then precipitating them by adding the solvent to a nonsolvent; although this method

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requires relatively simple, low-cost equipment, caution is necessary to avoid particle growth to microcrystals, which represents a problem.[30]

The top-down technologies are disintegration methods such as jet milling, pearl milling and HPH. A general problem of pearl mills is potential erosion of material from the milling pearls leading to product contamination.[31] Milling by HPH can be done by two principles: micro fluidization and piston-gap homogenizers. The obtained product is a suspension of drug nano-crystals in a liquid stabilized by a surfactant or polymer, showing an increased dissolution velocity and higher saturation solubility in comparison with micronized drugs[32]. The physicochemical properties are dependent on the type of stabilizer—that is, nonionic surfactants (e.g., polysorbates,poloxamines, and poloxamer) and ionic surfactants (e.g., bile salts and alkyl-sulfonates).To obtain a controlled-release dosage form with better physical stability, the nano-suspension has to be transformed into a solid, dry multiparticulate product, by means of lyophilization or spray-drying procedures. Lyophilization requires a cryoprotective agent added to the solution to avoid particle aggregation after reconstitution of the system.[33]

Spray-drying usually applies high temperatures in the process, which is not suitable for thermolabile drugs. Several drugs (e.g., cinnarizine, griseofulvin, indomethacin, itraconazole, loviride, mebendazole, naproxen, phenylbutazone,and, and phenytoin) have been formulated as nano-crystals for the evaluation of the Ostwald ripening effect as a function of the storage temperature. Except for indomethacin, after 3 months of storage at room temperature (22–25°C), Ostwald ripening occurred in all drugs. Lower temperatures were able to retard the ripening, whereas higher temperatures accelerated the effect.[34]

Lyophilization and spray-drying also affected particle agglomeration in particular for drugs with more hydrophobic surfaces, which were harder to disintegrate, and thus dissolution was compromised upon drying. The same was found for compounds having higher log P values. Drug nano-crystals can be considered as a universal formulation approach for poorly soluble drugs. The striking advantage is that the drug nano-crystals can be applied by various administration routes, including ophthalmic administration, to create systems with prolonged retention times; moreover, they constitute a simple system—simple to produce and simple to use. Currently there are few studies investigating NSAIDs in the form of nano-crystals for ophthalmic application, because the major prerequisite for nano-crystal formulation is the hardness of the drug crystals.[35]

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. Because of these properties, they can be used as an effective vehicle for ophthalmic drug delivery.[36]

Robinson et al 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[36]. 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

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tiers of branch cells with radial connectivity to the initiator core and an exterior or surface region of terminal moieties. So, greater possibilities can be explored by using dendrimers as ophthalmic drug delivery vehicles.[37]

Characterization of Nano sized delivery system

Nanometerology is the science of measurement at the nanaoscale and its application underlies all nanoscience and nanotechnology. The ability to measure and characterize materials as well as determine their shape ,size and physical properties at the nanosacale is vital for nano-material and devices. These need to be produced to a high degree of accuracy and reliability to realize the application of nanaotechnologies.

Four commonly used techniques are transmission electron microscopy (TEM), Scanning electron microscopy (SEM), Scanning probe electron technique (SPM) and Optical Tweezers(Single beam gradient Traps)

Transmission Electron Microscopy

TEM is used to investigate the internal structure of micro and nanostructure .It works by passing the electrons through the sample and then using magnetic lens to focus the image of structure in some case the individual atoms. TEM with high resolution transmission electron microscopy is the important tool for the study of nanoparticles[38].

Scanning electron microscopy

SEM uses the basic technology developed for TEM ,but the beam of electrons is focused to a diameter spot of approx 1nm on the surface of specimen and scanned repetitively across the surface. It reveals that the surface topography of the sample with the best spatial resolution currently achieved is on the order of 1 nm [39]

Scanning Probe Technique (Scanning Probe Microscopy)

SPM uses the interaction between a sharp tip and a surface to obtain the image the sharp tip is held very close to the surface to be examined and is scanned back and forth. As the tip is scanned across the sample, the displacement of the end of the cantilever is measured, using a laser beam. This can image insulating material simply because the signal correspond to the force between tip and the sample ,which reflect the topography being scanned .The scanning tunneling microscope brought a noble prize for physics to Gerd binning and Heinrich in 1986. The atomic force microscope uses this SPM technique, which reflects the surface topography of the samples.[40]

Optical Tweezers (Single Beam Gradient Trap)

Optical Tweezers uses a single laser beam to a spot on the specimen plane. The radiation pressure and gradient force from the spot create an optical trap, which hold a particle at its centre .Small inter-atomic forces and displacement can be measure by the technique .sample that can be analyzed range from single atom to micrometer –sized spheres to strand of DNA and living cells. Numerous traps can be used simultaneously with other optical techniques, such as scalpels, which can cut the particles being studied[41]

Future Perspectives

There are likely to be multiple applications of nanotechnology in ophthalmology. Nanotechnology can help in making nano devices for complex eye surgeries ,like glaucoma ,retinal vascular surgery, like glaucoma ,retinal vascular surgery and so on, also in the development of new lens materials for cataract treatment .It will also benefit the different delivery formats: injectables ,oral, implantable and so on. Moreover the development of different nanotechnology based tools can be used for

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improving imaging, screening and research techniques, including nanoarrays, nanolithography and mass spectrometry, which can be used in the fields of discovery of ophthalmic drugs. Besides this nanotechnology can also help to develop an effective and robust DNA nanoparticle therapy for the treatment of genetically based blinding diseases.

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