REVIEW ARTICLE

Nanomedicine and its role in Ophthalmology

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Abstract

In recent years, nanotechnology is rapidly emerging in the field of medicine. It has great potential in subfields of diagnosis, therapeutics and prophylaxis. It has created new and diverse avenues for development of new drug delivery system. In ophthalmology, due to unique and exposed nature of eyes nanotechnology has good prospects. In this article nanomedicine is review with special emphasis on ophthalmology.
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Introduction

In between life and death we suffer from number of diseases and it is rarest to rare that someone never faced illness in their entire life. For all those illness we take medicine either in the form of traditional drugs or modern medicines. As far as modern medicines are concerned they are the best available medicinal tools in this century as numbers of drugs are available for diagnosis, treatment and prophylaxis of diseases.

Targeted effects are observed with the use of these drugs but these end results depends mainly on efficacy and safety profile of the used drugs. These modern medicines have some major limitations like adverse effects which may occurs due to non specificity of drug action and lack of efficacy which is in many times due to improper or ineffective dosage formulation. Such as anticancer drugs causes bone marrow suppression, alopecia, nephrotoxicity and many other toxicities on organ systems. Similarly anti diabetic drugs have the problem of adequate glycaemic control as well as the difficulties with route of drug administration. In the field of diagnosis, various diagnostic tools are available. Sometimes these tools fail to provide enough data for complete diagnosis or early detection of the pathology like in case of cancers.[1]

Hence, we need the drugs which have best ability to target the specific pathological cells and the diagnostic tools which can have best degree of sensitivity. Such drugs will improve the outcome of disease condition with minimum adverse drug reactions. The diagnostic tools will be helpful in early and near accurate diagnosis. Nanomedicine shows some hopes for development of such kind of drugs and diagnostic tools which is nothing but the "utilization of nanotechnology for the benefit of human health and well being".[1]

Nanotechnology in Medicine

Zarbin MA et al (2010) in their study about Nanotechnology in ophthalmology extensively described the purpose of nanomedicine. They commented that "The aim of nanomedicine is the comprehensive monitoring, control, construction, repair, defense, and improvement of human biological systems at the molecular level, using engineered nanodevices and nanostructures that operate massively in parallel at the single-cell level, ultimately to achieve medical benefit".[2] The most important utility of nanotechnology in medicine is that it can target selective regions or systems thus increases efficacy of drugs and decreases their adverse reactions. Nanotechnology or nanomedicine is being used in many discipline of medicine including research and development. Its knowledge is being used in oncology, in cardiovascular diseases like removal of plaques and other applications. It is also used for repair

of bone and neural tissue. In diabetes, nanocomposite contact lenses can be used to monitor blood glucose level and beta cell can be transplanted by this technology. It has role in the treatment of fungal infections, viral infections, gene therapy, assisting stem cells to repair damaged tissue, for the research and development of biomarkers and at the level of molecular diagnostics. Its knowledge is useful for repair of pathological cell by manipulation of molecules on an individual basis. It has promising role for reversal of aging changes. Very focalized surgeries can be performed by using nanodevices. Drug discovery and new drug delivery systems are the other very important areas where it is used. In the field of diagnosis, it is being used as contrast agents, fluorescent dyes and magnetic nanoparticles.[1,3,4] Nanomedicine also has some safety issues as applicable to all newer technologies in the field of medicine. The concerns are with their route of administration as this nano materials can come into the contact of skin, lungs or intestinal tract. Another problem is about eliminations of these agents from the body. These materials can be deposited in organs leading to adverse consequences by altering the physiochemical properties of cellular and extracellular components.[3,5] Some authors observed toxicity at different organ system level.[6,7,8] Hence, before over enthusiastic use of these agents safety profile must be evaluated very well.

Current Status of Nanotechnology in Medicine

Nanomaterials are used as diagnostic and therapeutic agents as well as drug delivery devices. Examples are liposomes, emulsions, polymers etc.

Liposomes

Liposomes are the initial nanodrug delivery devices discovered in 1960 with limitation of rapid destruction by hepatic macrophages. They are lipid bilayer membranes having aqueous interior. Liposomes can also be of single lamella of membrane or multilamellar with multiple membranes. The molecules used for their preparations are similar to biological membranes, hence can be used to improve efficacy and safety of different drugs. Active substance if lipid soluble is located in lipid layer while water soluble in aqueous space. Amphotericin and hamycin, the cancer chemotherapeutic agents are delivered by Liposomes. New generation "stealth liposomes" have ability to escape macrophages due to coating and thus have longer half life.[1,3,9,10,11]

Emulsions

These are oil in water type mixtures which are stabilized with surfactant for maintenance shape and size. Active compound is emulsified in water phase. They are used for improving safety and efficacy.[12]

Polymers

These are polymer-drug or protein conjugates which reduce immunogenicity and increases half life. They increases permeability and provide stability to the compound even after endocytosis.[13,14]

Ceramic nanoparticles

These are made of ceramic nanoparticles like silica, titania and aluminia. They are biocompatible and used in cancer chemotherapy but have safety concern as they are non-biodegradable.[15]

Metallic particles

They are used as active or passive targeting agents. Generally they are supermagnetic in nature, such as iron oxide nanoparticles.[16,17]

Gold shell nanoparticles

These nanomaterials consist of dielectric core with thin shell of gold or metallic shell. These agents' posses good optical and chemical properties useful in biomedical imaging.[16] Nano shells are also useful in cancer chemotherapy and being investigated in diabetes.[18,19]

Carbon nanomaterials

In this group Nanotubes and Fullerenes fall. Nanotubes were discovered in 1991, they are tubular structures like a sheet of graphite rolled into a cylinder capped at one or both ends by a buckyball. They have excellent electrical conductivity and strength. Amphotericin B nanotubes are used in cancer chemotherapy with better efficacy.[20-23] Fullerenes are novel carbon allotrope having numerous points. They are used

as diagnostic agents but can stimulate fullerene antibodies.[1,3,24]

Quantum dots

They are semiconductor nanomaterials with fluorescent properties. They are used as diagnostic and therapeutic agents.[1,25]

Nanopores

These are high density pores with wafers and allow oxygen, glucose and insulin like materials. But prevents immunoglobulin from passing hence can be used as devices for protection of transplant from host defense system. In diabetic cases, β pancreatic cells can be transplanted by these devices.[26]

Nanobubbles

They are bubbles like nanomaterials in which anticancer drugs can be incorporated. They can selectively target tumor cell under the influence of ultrasound exposure. Rapaport used doxorubicin by this method.[1,27]

Dendrimers

These nonomaterials have regular branching pattern, the number of which can be controlled depending upon the need. It has spherical structures from which branches arise and makes cavities which can be used for transport of drugs in targeted cancer cells.[23,28]

Respirocytes

These nanodevices are artificial red blood cells with censors on the surface which can be monitored on computer screen. Have 236 times more oxygen supplying capacity in unit volume and time in comparison to red blood cells.[27]

Microbivores

They are artificial white blood cells having property to circulating microbes in blood stream.[29]

Application of Nanotechnology in Ophthalmology

Nanotechnology has very promising role in ophthalmology as eye is a very good example for use of nanotechnology since it is easily accessible, small and exposed organ. It can be used for the management of oxidative stress, for measuring intraocular pressure, to treat choroidal new vessels. It can be used in glaucoma for prevention of post operative scarring. It also has important role in treatment of retinal degenerative disease with gene therapy; prosthetics; and regenerative nanomedicine.[2]

Drug delivery system

Many ophthalmic conditions can be treated by instilling eye drops over the ocular surface. But unfortunately less than 5% instilled drugs penetrates cornea because of presence of many lipophilic and hydrophilic static and dynamic barriers such as layers of cornea, sclera and retina, choroidal/ conjunctival blood flow, lymphatic clearance, rapid tear turnover, blinking, solution drainage, vitreous and many more between the surface of the eye and the treatment site for their absorption. Moreover, tear dynamics and drug dilution due to reflexive tearing also decreases drug absorption leading to diminished efficacy of the drugs. Hence, more frequent instillations of eye drops even more concentrated are needed for maintenance of therapeutic drug level at pre-corneal surface. Such eye drops may induce local toxicity, corneal dryness and sometimes systemic side effects. Nanomaterials are better alternatives to traditional eye drops or ointments as far as drug delivery to eye through ocular surface are concerned. The superiority is because of their small size and amount which makes them more tolerable including less reflexive tearing and decreased incidence of blurring hence increasing the efficacy of drugs. These nanodrugs must be bioadherent and biodegradable for better efficacy and safety.[30,31,32]

- ***Nanoparticles:*** Nanoparticles are mainly useful for the management of chronic ophthalmic conditions just like glaucoma, retinal edema, uveitis and ocular neovascularization.
- ***Liposomes:*** They can deliver both hydrophilic and lipophilic drugs.[30]
- ***Dendrimers:*** These nanomaterials can be used for delivery of many drugs like pilocarpine, vacular endothelial growth factor inhibitors and antimicrobial agents such as gatifloxacin.

Nanomaterial-dendrimers if formulated in adhesive form can be used as adhesive agents for corneal repair and other ophthalmic repair in

which adhesives are required. Such dendrimers has great potential as alternative to suturing material for penetrating ophthalmic injuries.[31,32] Electrostatic interactions occur between charged nanopolymers and mucins of tears making them mucoadhesive. By such mucoadhesive polymers drugs can be retained for longer duration at ocular surfaces.[33] Quinolones have the problem of low solubility and destructive in nature for corneal epithelium. Cheng *et al*[44] prepared dendrimer encapsulated fluoroquinolones such as nadifloxacin and prulifloxacin and resolved the problem of low solubility.

In 1981 Smolin G et al showed that liposome encapsulated idoxuridine have better corneal penetration ability and much better efficacy in comparison to free drug solution in Herpetic keratitis.[35] Dharma SK et al also observed better corneal penetration of liposome-encapsulated idoxuridine in comparison to regular form of the drug idoxuridine in New Zealand albino rabbits for a time interval of 6h.[36] Kaur IP et al, Ebrahim S et al and Bochot A and Fattal E also extensively reviewed utility and efficacy of liposomes for ocular drug delivery and found much better in comparison to the routinely used uncapsulated drugs in various ophthalmic conditions.[37,38,39] Nanoparticle-drug loaded contact lenses were studied by Chauhan et al. They observed extended drug delivery, better corneal bioavailability and improved patient compliance.[40] Molecularly-imprinted silicone hydrogel contact lenses were prepared by Byrne et al for delivery of small molecule such as ketotifen fumarate and large molecules such as high molecular weight hyaluronic acid and found better bioavailabilty.[41,42] Peng CC et al successfully treated glaucomatous dogs with inherited open angle glaucoma by using timolol with silocone hydrogel contact lenses and found requirement of only one-third of the drug in comparison to routinely used eye drops for similar efficacy.[53] Nanomaterials can be used to prolonged residence time, to prepare sustained release formulation and the inhibit efflux proteins on the cornea. Such nanomaterials can improve the therapeutic efficacy of ophthalmic drugs.[44]

Cataract

Reactive species are important causes of cataract. Nanosubstances have a high surface area to volume ratio. This property of nanomaterials can be used for removal or for decreasing the reactive species, thus useful in cataract and other ocular disease.[45] Cerium oxide (CeO2) nanoparticles (nanoceria particles) have a big surface area to volume ratio which is very useful for scavenging reactive oxygen intermediates (free oxygen radicals).[46] Junping Chen et al observed prevention of light damage in rodent by intravitreal injection of nanoceria particles. It indicates promising role of this nanotechnology for the management of other oxidative damaged ophthalmic conditions like macular degeneration and diabetic retinopathy.[46] Cetinel S et al suggested nanotechnology for the management of cataract. They opined that nonsurgical management of cataract can be done by promoting protein solubility and/or dissolving fibrillar aggregates.[47] Natural antioxidant such as flavonoids, phenolic acids, carotenoids and vitamins has a role in prevention of cataract. Sunkireddy P et al opined that by nanobiotechnology, therapeutic potential of these natural antioxidant molecules can be enhanced by increasing the solubility, stability and bioavailability.[48] Thiagarajan R and Manikandan R commented that curcumin is well known antioxidant anti, anti-cataract agent. But the problem with this agent is it has less bioavailability which can be taken care very well by delivery of this agent by nanodrug delivery system.[49]

Glaucoma

Nanotechnology has potential for expanding diagnostic, imaging and surgical modalities in glaucoma including improvement in drug bioavailability, can exploit other targets like retinal ganglion cells neuroprotection, can halt the progressive loss of retinal ganglion cells and gene therapy can be used more effectively for more permanent treatment of glaucoma.[50] In glaucoma, fluctuation of intraocular pressure occurs. Monitoring of intraocular pressure at various time intervals is one of the parts of glaucoma management. By nanotechnology it is possible to continuously monitor the intraocular pressure. A contact lens with sensor is prepared by Matteo Leonardi in Switzerland. The sensor records changes in curvature of cornea brought by fluctuation of intraocular pressure. Christoph F and Georg M have successfully evaluated this

sensor among 11 patients for intraocular pressure. The recorded intraocular pressures were either flat, fluctuating or that had spikes.[51,52,53] Natarajan JV et al prepared sustain released latanoprost and successfully tested in vitro and also observed sustained efficacy of lowering the intraocular pressure for 120 days in a diseased nonhuman primate model. The carrier for latanoprost delivery was nanosized unilamellar vesicle. They opined that such carrier can be used for other ophthalmic conditions also.[54]

Gene Therapy

Gene therapy can be used through cornea as it is relatively separated from systemic immune system. Gene can be transferred through cornea for structural functions or for modulating pathological conditions. Gene therapy can also be used for prevention of cornea rejection, cornea neovascularization and herpetic stromal keratitis.[55] Nanoparticle-based gene therapy is effective for continuous delivery of therapeutic genes and better efficacy because of improved cellular uptake, endosomal escape and transport up to the nucleus.[44]

Nanotechnology and Retina

There are many factors which affects availability of drugs at retina such as particle size, composition, surface charge and mode of administration. Sakurai et al[56] studied well-defined fluorescently-labeled polystyrene nanoparticles in pigmented rabbit model while Yu et al investigated biodistribution of C57BL/6 in mice model.[57] They have not observed any histopathological toxicity or structural damages to the retinal structures. Nanoparticles have good potential to be used as drug or gene carriers for retinal disorders if suitably engineered with appropriate surface chemistry.

Safety Issues

Nanoparticles also have some safety issues as they are in extreme microscopic in nature which not only provide them many advantages but also have potential hazards similar to particulate matter. These agent can cause varied pathologies of respiratory, cardiovascular and gastrointestinal system if used injudiciously and due care is not taken.[1] As far as ophthalmic issues are concerned, appropriate design of nanoparticle size, chemistry and surface dynamics can reduce risks. Naash *et al* investigated CK30PEG-DNA nanoparticles in a mouse model by subretinal injection. They have not observed any infiltration of neutrophils or lymphocytes, or elevation of cytokines in the retinas. Although initial, inflammatory response was seen it was returned back to normal within 2 days post-injection. They also observed it as safe even after repeated dosing.[58]

Conclusion

Nanotechnology has a promising role in medicine. Expectations are high with this new branch of medicine. It has endless potential benefits. But safety still not fully evaluated. It should be fully and adequately evaluated and risk benefit issues must be balanced before its application. In ophthalmology it has huge potential due to unique and exposed nature of eyes. Nanomedicine has created new future of therapeutic, diagnostic and molecular research.

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