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Review Article

Advances in Nanoscience and Nanotechnology

Ocular Tissue Engineering and Regeneration: Nano Biomaterial Applications

Param Patel*, Dhruv Patel*, Shyam Patel*, Dewi Melani Hariyadi#, Umi Athiyah# and Yashwant Pathak##*

*College of Pharmacy, University of South Florida, 12901 Bruce B Downs Blvd, MDC 030, Tampa FL 33612, USA

#Faculty of Pharmacy, Airlangga University, Surabaya, Indonesia

##Adjunct Professor, Faculty of Pharmacy, Airlangga University, Surabaya, Indonesia

***Corresponding author**
Yashwant Pathak, College of Pharmacy, University of South Florida 12901 Bruce B Downs Blvd, MDC 030, Tampa FL 33612, USA, E-mail: ypathak1@health.usf.edu

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Abstract
In new ocular drug delivery, nanoparticles are designed to overcome the barriers, while increasing the drug penetration at the target site and prolong the drug levels by few internals of drug administration in much lower doses without any prolonged toxicity that conventional eye drops offer. Nanoparticles offer high specificity and multi-functionality DNA, that can be resulted in higher transfection efficiency for gene therapy. Fibrin; a versatile scaffold for tissue engineering applications combines cell and molecular biology with materials and mechanical engineering to replace damaged or diseased organs and tissues. Fibrin plays an important component in homeostasis, which has been used extensively as a biopolymer scaffold in tissue engineering. Fibrin has been used in combinations with other materials and is used as a biological scaffold for stem or primary cell regeneration for adipose tissue, bone, and cardiac tissue, etc. Therefore, fibrin is a versatile biopolymer, which has shown great potential in tissue regeneration and wound healing. Nanotechnology is transforming biological engineering, on a much smaller scale as shown in research. In large, cases relating to corneal infections has been increasing and nanomedicine has shown a long lasting and profound treatment relating to corneal infections but not only subject to this infection. Ocular engineering has been on the rise with nanomedicine involvement.

Keywords: Fibrin Glue, Retinal Progenitor Cells, Encapsulation, Cell Delivery

Introduction
Nanomaterials have been found useful in the use of ocular tissue engineering as they have the capability to assume the shape of fill the defective or missing tissues necessary in biological processes. Nanomaterial substitutes can supply the necessary physical properties required in ocular tissue [1]. Nanotechnology requires materials and devices to be created and used at a specific intracellular and molecular size of an order of <100 nm. The goal of nanotechnology in ocular tissue engineering is to improve human biological systems at a molecular using nanostructures and nanodevices that operate a single cell level [2]. As of recent, there has been an increase in the number of scientists that have turned to the use of nanomaterials to overcome barriers and challenges faced by conventional methods [3]. Recent nanomaterials used in the application of ocular tissue engineering are but not limited to polymeric micelles, liposomes, dendrimers, niosomes, hydrogels, cyclodextrins, fibrin, and elastin like polypeptides [1, 3, 4].

Field of Nanomedicine
Nanomedicine is a field of medicine where nanoscale delivery systems are used to treat various illnesses. Nanomedicine in general offers many advantages compared to conventional drug delivery methods. Some advantages are that the drugs can be targeted to a specific tissue, more efficiency in delivering nonpolar and large drugs, less side effects, and proper delivery of therapeutic substances. Overall, the aim of nanomedicine is to improve the overall quality of life and reduce as many illnesses as possible [5].

Fibrin Scaffolds for Ocular Tissue Engineering
Ocular tissue engineering requires the proper use of transplantation. Research indicates that issues such as the body's immune system rejecting the organ or finding a donor are minimised when using this type of cornea transplant. Fibrin is a prime product that is used to treat many corneal diseases such as limbal cell deficiency and corneal perforation. Patients that have these conditions are able to get treated by using glue composed of fibrin along with an amniotic transplant so that the cornea can be fixed. This is done by encapsulating corneal epithelial stem cells into the fibrin infused gel and is done *in vitro*. Aprotinin is used as an inhibitor so that the fibrin gel does not degrade. Research on rabbits indicates that the cornea was fully transplanted and that the epithelial, endothelial, and stromal were layered sequentially to get a replica of a human cornea. Table 1 describes the possibility of different engineered tissues from Fibrin and fibrin based products.

Table 1: Possibility of different engineered tissues from Fibrin and fibrin based products

Engineered Tissue	Fibrin Hydrogel	Fibrin Glue	Fibrin Micro- heads
Adipose tissue	Yes	Yes	No
Bone	Yes	Yes	Yes
Cardiac tissue	Yes	Yes	No
Cartilage	Yes	Yes	No
Liver	Yes	No	No
Muscle tissue	yes	No	No
Nervous Tissue	Yes	Yes	No
Ocular tissue	Yes	Yes	No
Skin	Yes	Yes	Yes
Tendons and Ligaments	Yes	Yes	Yes
Vascular tissue	yes	Yes	No

(Table 1 data is based on information published in reference 4, Ma, Zuwei. et al. Potential of Nanofiber Matrix as Tissue-Engineering Scaffolds. 2005. Tissue Engineering, Vol. 11. pp. 101-109)

Fibrin and collagen can be used in conjunction to replicate the thickness of a human cornea, its vascularity, and position of the cornea with the sclera [4]. With the application of fibrin glue and cells that use the spray system comes with multiple advantages creating a thin homogeneous film of fibrin glue that costs the surface extensively using only a small amount of fibrin glue and localizing the proliferating cells to the area of the wound.

Nanomedicine is advancing through the use of nanomaterials at an increasing rate. For ocular drug delivery systems, it is essential that the treatments can be used for the targeted tissues. Some of the nanomaterials that are used, are very versatile in their ability to be administered to the ocular tissue. Any use of nanomaterials for tissue engineering purposes must replace the defective tissue, be able to sustain various cellular processes for regeneration of new tissue, allow for proper exchange of wastes and nutrients, be able to physically sustain the tissues physical requirements, and stay in the target area until intended.

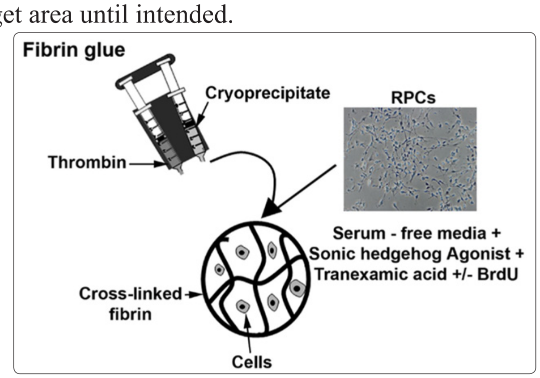

Figure 1: Diagram showing the preparation of fibrin –encapsulated RPCs. Aliquots of cryo- precipitated fibrinogen and thrombin and retinal progenitor cells were combined and allowed to polymerize (with thrombin serving as a cross linker) The encapsulated cells were then cultured in serum free media with additives such as sonic hedgehog agonist, transexamic and BrdU (Reference Figure taken from Front. Bioeng. Biotechnol., 03 February 2015 | https://doi.org/10.3389/fbioe.2014.00085) with permission

A major obstacle in nanomaterial applications is that although some nanomaterials have advantageous properties, they are not able to meet all the requirements necessary for maximum sustainability. For example, polymers that are synthetic are biocompatible, however they do not attach properly to the tissue and often times do not help with growth. In contrast, polymers that are found naturally are good for bio-signaling, but at times are antigenic and can be difficult to regulate [1].

Dendrimers are globular polymers that range from 3-20nm and have a definite shape. Some of them have antimicrobial uses and can be used as successful drug delivery systems. They have properties that allow them to form a layer on top of the cornea. These dendrimers do not limit vision and they reduce the toxicity of the corneal cells. Dendrimers can also be used with hydrogels as they offer more side groups that are able to cross link when the polymer concentrations are low. Formulations such as these are able to close out corneal lacerations for eyes that are porcine enucleated [5].

Elastin-like polypeptides (ELPs) are widely used for nanomaterial engineering because they are non-immunogenic, biocompatible, and biodegradable. Scientists have used ELPs also because their molecular weight and amino amino acid sequence is easy to manipulate as needed at both the synthetic and genetic level. This allows for the ELP to function at its optimum level [1].

Liposomes are spherical vesicles that have lipid bilayers and an aqueous inner core. They are used in many ocular drug delivery applications. When idoxuridine is encapsulated inside liposomes, there is ease of penetration into the cornea for drug delivery. Nanospheres to the contrary are around 360nm and promote nerve regeneration when used for ocular delivery. Nanospheres that have the epidermal growth factor receptor (EGFR) are able to help with nerve regeneration due to their compatibility with the optic nerve [5].

Nanotechnology in Ophthalmology

Nanotechnology is a revolutionary sub-field in bioengineering that aims to comprehensively observe, defend, repair, and improve human biological systems on a micro level. As it has gotten progressively larger, the uses of nanotechnology have expanded to many fields and benefited science greatly. The uses of nanoparticles in ophthalmology are extensive: treating choroidal new vessels, medicating retinal degenerative disease with gene therapy, preventing scarring post-glaucoma surgery, in regenerative nanomedicine.

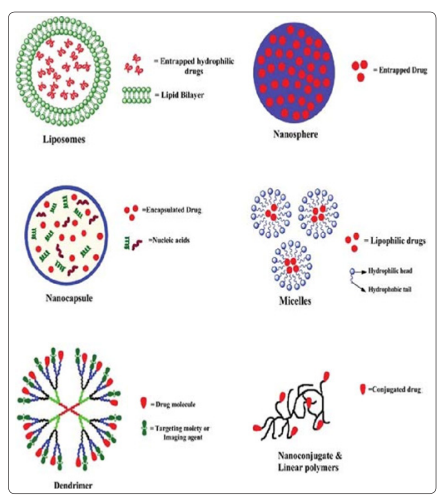

Figure 2: Different types of nanoparticles used for drug delivery

to eye figure taken from Reference 5, Xu, Q, Kambhapati,SP, Kannan, RM, Nanotechnology approaches for ocular drug delivery, Middle East African Journal of Ophthalmology, DOI:10.4103/0974-9233.106384, 2013, with permission

The overall goal is to be able to tackle the therapeutic challenges (drug delivery and postoperative scarring) that we face today and nanotechnology gives us the tools to be able to do so. However, we continue to face obstacles with nanotechnology, mostly in sustainability and biocompatibility [8]. Recently corneal and topical infections have led to a rise in the number of corneal surgeries for cataracts, glaucoma, and an increase in contact lense use. Ocular infections pose severe issues for patients causing corneal reddening, opacification, irritation and inflammation, rupture; these issues can lead to impaired vision and possibly permanent blindness if not treated correctly. Nanomedicine has offered a way to improve drug delivery in order to medicate individuals effectively. Systems that improve drug residence time on the corneal surface have a profound positive impact. This can lead to increased drug absorption through periocular tissue to reach inner ocular tissues. One of the most proficient methods for nanomedical drug delivery in ocular tissue is through drug-eluting contact lenses, many of which decrease the frequency of drug administration [7].

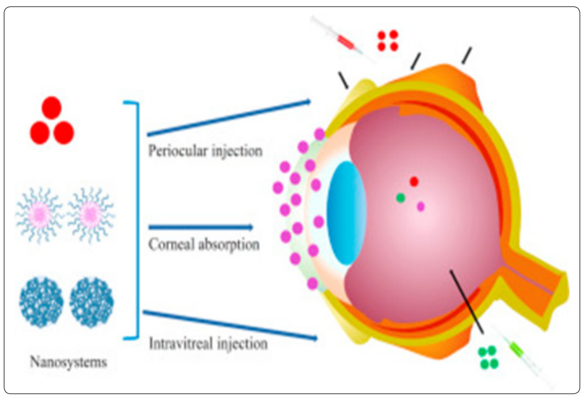

Figure 3: Schematic diagram of drug delivery using nano carriers to the posterior eye using drug nano carriers and injecting in the posterior eye

One way that scientists have been using to peer into the problem of biocompatibility is to investigate the bio-distribution of nanoparticles in the retina. The use of bio-distribution provides an understanding into the bioavailability, duration of drug action, cellular uptake, and toxicity. Issues with cellular uptake and toxicity arise frequently with nanoparticles. Scientists have been thoroughly researching this to find ways to eliminate these problems.

Conclusion

Overall, research has shown that nanomedicine as well as nanoparticles are moving forward with biotechnology to help cure many diseases and health problems. Nanomedicine in research has shown phenomenal results, suggesting that things could be altered or repaired in ways that would cause less toxicity to the human body. Studies have shown that nanoparticles have been found to be useful in the use of ocular tissue engineering, since nanoparticles can assume the shape or fill defective or missing tissues that are necessary for biological processing (Figure 4). We saw that there was a common goal for nanotechnology in ocular tissue engineering, and that is to improve the biological system at a molecular level using nanostructures and nanodevices that operate at a single level within a cell. Although, the main focus of this research was ocular engineering using nanomedicine, it is also delivered to treat various illnesses. Comparatively, nanomedicine has many advantages oppose to conventional drugs and has a higher efficiency in delivering nonpolar and large drugs with less side effects, and a direct delivery of therapeutic substances. Research has also shown an increase in corneal and topical infections causing the need for surgeries or other conventional procedures, with the help of nanotechnology researchers have been able to reduce conventional drugs and leave a prolonged effect. Although there are still problems that are being possessed with nanomedicine and nanoparticles in medicine, due to the bioavailability and biocompatibility.

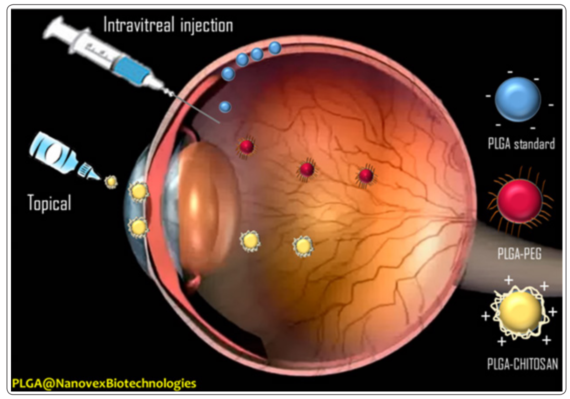

Figure 4: Nano drug delivery injextions to the posterior and anterior eye using PLGA nanoparticles (Figure taken from http://www.nanovexbiotech.com/plga-nanoparticles-ocular-drug-delivery/ with permission)

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