Ophthalmology Research: An International Journal
4(1): 9-15, 2015, Article no.OR.2015.022
ISSN: 2321-7227

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Applications of Thin Films in Ophthalmology

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Authors' contributions

This work was carried out in collaboration between all authors. Authors LL and AK collected the literature and prepared the manuscript. Authors VK and IT organized the structure of the review and contributed to the bibliographic search. Authors SL and SD revised it critically. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/OR/2015/18081
Editor(s):
(1) Rachid Tahiri Joutei Hassani, Ophthalmology Department III, XV – XX National Ophthalmologic Hospital, France.
Reviewers:
(1) Rahmi Duman, Bursa Sevket Yilmaz Training and Research Hospital, Department of Ophthalmology, 16800, Bursa, Turkey.
(2) Anonymous, Finland.
Complete Peer review History: http://www.sciencedomain.org/review-history.php?iid=1021&id=23&aid=9006

Mini-review Article

Received 1st April 2015
Accepted 15th April 2015
Published 27th April 2015

ABSTRACT

Nanotechnology provides a revolutionary approach to therapeutic challenges. Drug delivery, gene therapy, novel diagnostic methods and tissue engineering rank among the main fields of current nanomedical research. Thin films, with their unique optical and mechanical properties, are regarded as valuable biomedical tools and research is conducted to incorporate them in a variety of nanomedical devices. Main applications of thin films in ophthalmology include intraocular drug delivery, coatings for intraocular implants, scaffolds for retinal and corneal tissue engineering, novel diagnostic methods and modified intraocular lenses. A variety of chemical substances and nanotechnology techniques are used to fabricate thin films for ophthalmic use and it is clear that this burgeoning field may overcome hurdles and produce significant results that will revolutionize our approach to ocular diseases.

Keywords: Thin films; nanotechnology; ophthalmology; diagnosis; drug delivery; therapy.

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1. INTRODUCTION

Nanomedicine represents a multidisciplinary scientific field with promising perspectives in the fields of diagnosis and treatment of a broad variety of diseases [1]. Tissue engineering [2], drug delivery [3], novel imaging and diagnostic methods [4] and gene therapy [5] rank among the most important applications of Nanomedicine and commercialization efforts are expected to increase rapidly within the following years.

Ophthalmology is viewed as one of the medical specialties with the greatest potential to incorporate Nanotechnology advancements [6]. Relatively small size of the eye, the blood-ocular barrier and low permeability of drugs through the cornea, the conjunctiva and the sclera render ocular diseases excellent candidates for research at the nanolevel. Significant progress has been recorded during the last decades and development of revolutionary treatments for a number of ocular diseases is currently under way. Intraocular drug delivery nanosystems [7], corneal and retinal tissue regeneration [8], noninvasive diagnostic techniques [9] and gene therapies [10] with the use of nanoparticles lie at the epicenter of current research. It is reasonable to expect that Nanotechnology will enable us to address sight-threatening diseases such as age-related macular degeneration (AMD) and glaucoma in the future.

Thin films, developed and characterized with Nanotechnology methods, are commonly used as biomaterials because of their unique interfacial and mechanical properties. Application of thin films in medical specialties such as cardiology [11-13], orthopedics [14] and urology [15,16] leads to new approaches to therapeutic challenges. Obstacles related to safety and cost-effectiveness of nanotechnology research remain, however those are not insurmountable and thin films are expected to contribute significantly to biomedical research.

Primary aim of this review is to summarize and discuss applications of thin films in diagnosis, monitoring and treatment of ophthalmic diseases.

2. DRUG-ELUTING CONTACT LENSES

Low efficiency of ophthalmic drops is a common problem in Ophthalmology. Although they account for the vast majority of ophthalmic medications, they do not achieve a steady and uniform therapeutic concentration. Their absorbance is relatively low, they cause side effects related to the ocular surface and patient compliance tends to be insufficient.

Ciolino et al. [17] have suggested a drug eluting contact lens as an alternative drug delivery system. They have fabricated a prototype lens consisting of a thin film of poly (lactic-co-glycolic) acid (PLGA) that contained the drugs, coated by poly (hydroxyethylmethacrylate) (pHEMA). This dual polymer system provided zero-order kinetic drug release of ciprofloxacin and fluoroscein over a period of four weeks and therapeutical concentrations were achieved. It is underlined that storage of the prototype lenses is an issue that remains to be addressed.

3. COATINGS FOR INTRAOCULAR IMPLANTABLE DEVICES

Retinal photoreceptors degeneration ranks among the main causes of irreversible blindness. Retinal implants are viewed as a possible solution to this sight-threatening situation and great progress has been recorded in the design and fabrication of implantable stimulating devices. Li et al. [18] have developed biocompatible ultrananocrystalline diamond thin films to encapsulate intraocular implants, enabling ophthalmic surgeons to place them inside the eye without the risk of damaging interaction with the tissues. They have also fabricated bioinert materials with high dielectric constant based on Al_2O_3 and TiO_2 nanolaminate structures and they have produced high-capacitance capacitors which are necessary to allow intraocular implantation of the artificial retina. It is noteworthy that these advances may also be applied in other implantable biomedical devices.

Glaucoma is also a major cause of blindness worldwide. It refers to a group of ocular disorders that may lead to peripheral vision loss and eventually to loss of central vision. Although in most cases eye drops, if administered properly, provide a sufficient treatment, surgical treatment is often necessary. Implantation of glaucoma drainage devices (GDD), such as Ahmed glaucoma valve, may lead to satisfactory results, but fibrosis represents a common complication that reduces their success rate. Ponnusamy et al [19] have designed and manufactured porous mitomycin C (MMC) and 5-fluorouracil (5-FU) releasing thin films of PLGA, using a spin-coating technique. The double-layered biodegradable films provided a continuous release of antifibrotic

drugs for a period of 28 days and may be used as coating for GDD implants.

4. DIAGNOSTICS

Optical coherence tomography (OCT) is a valuable tool that allows diagnosis and monitoring of a number of ophthalmic diseases, such as AMD, diabetic retinopathy and glaucoma. The growing impact of OCT on management of ocular diseases underlines the necessity of standardized assessment of OCT devices. According to Baxi et al. [20], thin films may contribute to the standardization process. Their research has led to the development of a retina-simulating phantom, consisting of thin scattering films of polydimethylsiloxane (PDMS), that mimics the optical properties and structure of retinal layers. Spin coating and laser etching were the methods that were applied in the fabrication of the phantom, which displayed promising results.

5. CORNEAL TISSUE ENGINEERING

The cornea is the outermost layer of the eye and it serves as a protective barrier for the eye, providing also over two thirds of its refractive power. Corneal disease may lead to blindness, with corneal transplant being the only therapeutic method in many cases. Corneal transplants' relatively high rate of rejection and failure and shortage of donors are obstacles that could be overcome with the development of an artificial cornea.

Young et al. [21,22] have conducted extensive research on cornea bioengineering. They have developed membranes consisting of chitosan and polycaprolactone (PCL) which may serve as a biocompatible scaffold for corneal endothelium. Endothelial cells demonstrated a satisfactory proliferation and they formed a continuous layer. Lawrence et al. [23] prepared optically transparent thin silk films and investigated their suitability for culture of corneal fibroblasts. While further research is deemed necessary, silk film biomaterials demonstrated promising results as scaffolding for corneal tissue.

Collagen has also been used to prepare corneal scaffolds. As Crabb et al. [24] have demonstrated, collagen films displayed suitable mechanical properties and may be used to produce bioengineered corneal stroma. Ozcelik et al. [25] developed poly(ethylene glycol) (PEG)-based hydrogel films with satisfactory optical and mechanical properties. These biocompatible, biodegradable films allow proliferation of corneal endothelial cells on their surface.

6. INTRAOCULAR DRUG DELIVERY SYSTEMS

Intraocular drug delivery represents a major challenge to scientists because of the unique anatomical and physiological characteristics of the eye. Nanomedicine advancements have been used to overcome obstacles such as the blood-ocular barrier and low permeability of ophthalmic tissues and to lead to more effective and convenient treatment of ophthalmic diseases. PCL thin films are often used in intraocular drug delivery applications and it has been demonstrated by Bernards et al. [26] that they are safe, structurally stable and well-tolerated.

Thin films have also been applied in novel methods of glaucoma pharmaceutical treatment. Huang et al. [27] prepared PLGA films loaded with timolol and observed a satisfactory intraocular pressure (IOP) lowering effect. Okuda et al. [28,29] developed a honeycomb- patterned thin film that can be used in filtration surgery in glaucoma patients that fail to respond to medication. In vivo experiments in rabbits illustrated that the poly (L-lactide-co-epsilon-caprolactone) thin film successfully protected the conjunctiva from MMc and reduced bleb avascularity.

Posterior capsule opacification (PCO) or secondary cataract, as it is also known, is a common complication of cataract surgery and it has been suggested that modified intraocular lenses (IOLs) may contribute to its prevention. Liu et al. [30,31] designed and fabricated PLGA thin films that were loaded with rapamycin and were developed on the surface of IOLS. *In vivo* experiments demonstrated satisfactory anti-inflammatory and anti-proliferative results.

7. RETINAL SCAFFOLDS

Retina is a unique tissue and it is involved in the vision process. Retina contains neural cells that are very sensitive if changes occur to the retinal environment. Therefore, the presence of the physiological barrier structure, the blood-retinal barrier (BRB), is of imperative importance in order to maintain optimal retinal homeostasis [32].

The BRB consists of the inner and the outer BRB. The tight junctions of the retinal endothelial cells that are covered by pericytes and glial cells form the inner BRB, while the outer BRB is formed by the tight junctions of retinal pigment epithelial cells (RPE) and the choriocapillaries that are fenestrated. [33] More specific, the retinal endothelial cells of the inner BRB form a tightly sealed monolayer, separating the retinal from blood side of the endothelium, and thus prevent paracellular transport of materials between the retina and the circulating blood. This paracellular impermeability of hydrophilic molecules is governed by the tight junctions in the healthy retinal capillary endothelium and the desirable molecules are transported to the retinal cells by a transcellular route. [34] These unique anatomical and physiological features of the retina impart the difficulties of a drug to reach and act through the circulating blood to the retinal cells. For these reasons, in the majority of the retinal diseases the drug is injected in the eye via pars plana, in the vitreous cavity.

AMD is the leading cause of blindness in patients over the age of sixty in United States of America. [35] Patients suffering from AMD have 10-15% risk of severe central vision loss. The majority of the these patients (75%) lose their vision due exudative AMD, which is characterized by choroidal neovascularization that invades Bruch's membrane and causes intraretinal hemorrhage and damage to the RPE. [36] Exudative AMD could be effectively treated with anti-vascular endothelial growth factors (anti-VEGF), which are injected in the vitreous cavity.

Bruch's membrane and RPE cells compose the outer retinal layer and perform a crucial role in maintaining photoreceptor viability. Degeneration of RPE cells and Bruch's membrane may lead to accumulation of metabolic cell products and decreased level of nutrient transport to the photoreceptors. [37] These alterations have impact on photoreceptor function and may affect visual acuity. A potential treatment of non-exudative AMD should prevent the degeneration of RPE cells and prevent also the alterations of Bruch's membrane. Potentially, replacing the outer retina with healthy RPE cells could prevent the damage to the photoreceptors.

Thomson et al tried to manufacture thin films of poly (L-lactic acid) (PLLA) and PLGA 75:25 and 50:50 biocompatible and biodegradable materials. [38] These materials were shown to be non-toxic when employed intraocularly for drug delivery purposes. [39] Furthermore, their degradation products are removed from the body through either the respiratory or the urinary systems. [40] PLLA and PLGA are approved for specific human clinical uses by the Food and Drug Administration. [41] The investigators manufactured the thin films using solvent casting technique. PLLA thin films could not be removed from the glass surface and they were not suitable for further experiments. PLGA films were easily removed. Despite the films were non-porus, RPE cells were found to attach on these substrates when cultured *in vitro* [38].

Other researchers design a synthetic biodegradable polymer substrate with specific chemical micropattern from PLGA and diblock copolymers of poly (ethylene glycol) and poly (DL-lactic acid) (PEG/PLA). [42] Previous experiments demonstrated that RPE cells cultured on PLGA films formed cell monolayers. [43] In order to improve RPE function, a microcontact printing technique was used to obtain thin films chemically micropatterned surfaces. The model thin films contained organized arrays of unmodified glass domains of micrometer scale separated by regions modified with octadecyltrichlorosilane (OTS) self-assembled monolayers. The investigators observed that the RPE cells cultured on these thin films retained their characteristic cuboidal morphology [42].

Tezcaner et al. [44] manufactured thin films from poly (hydroxybutyrate-co-hydroxyvalerate) (PHBV) in order to culture RPE cells. PHBV has been found to exhibit low toxicity and well tolerated by the tissue when implanted subcutaneously. No inflammation, abscess formation or tissue necrosis was observed in tissues adjacent to this material. The researchers manufactured thin films using solvent casting technique and functionalized the surface by oxygen plasma treatment. The investigators observed that RPE cells grown to confluency as an organized monolayer in treated PHBV thin films [44].

Lu et al. [45] tried to design a scaffold that mimic the Bruch's membrane in order to culture RPE cells. The film was made of cross-linked collagen fibers and exhibited diffusion properties, which allow the flow of nutrients and waste of RPE cells. The researchers also observed that the attached on the collagen film RPE cells formed an epithelial phenotype capable to phagocytize photoreceptor outer segments.

Other investigators designed thin films as scaffolds for RPE cells from polyurethanes. [46] Biodegradable polyurethanes, derived from poly (caprolactone), poly (ethylene glycol), isophorone diisocyanate and hydrazine have been developed by producing water dispersion of the polymers, following by a drying step and thus the usage of organic solvent is avoiding. [47] Also, these polymers displayed high elasticity and biocompatibility and they can be manufactured with the desirable thickness. [48] The researchers manufactured the thin films by casting the polymer dispersions in a Teflon mold and allowing them to dry in room temperature for one week. Culture experiments using RPE cells demonstrated the formation of an organized monolayer of cells, which exhibited polygonal appearance and the establishment of cell-cell interaction. Also, these thin films display the desirable mechanical properties for an easy transcleral-driven subretinal implantation [46].

8. CONCLUSION

Nanotechnology advancements play an increasingly significant role in ophthalmic research. It is safe to predict that nanodevices will contribute to the development of new diagnostic and therapeutic strategies in the future. Thin films technology is a valuable tool in the fabrication of nanomedical devices and it is likely to offer solutions to otherwise intractable problems. It is clear that issues such as safety and cost-effectiveness still need to be addressed. However, applications of thin films with their unique properties in Ophthalmology are expected to lead to revolutionary changes.

CONSENT

It is not applicable.

ETHICAL ISSUE

There are no ethical issues in this review.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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http://www.sciencedomain.org/review-history.php?iid=1021&id=23&aid=9006