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Minireview Article
Applications of Thin Films in Ophthalmology

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*

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.

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

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42 **1. DRUG-ELUTING CONTACT LENSES**

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

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

55

56 **2. COATINGS FOR INTRAOCULAR IMPLANTABLE DEVICES**

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

67 Glaucoma is also a major cause of blindness worldwide. It refers to a group of ocular
68 disorders that may lead to peripheral vision loss and eventually to loss of central vision.
69 Although in most cases eye drops, if administered properly, provide a sufficient treatment,
70 surgical treatment is often necessary. Implantation of glaucoma drainage devices (GDD),
71 such as Ahmed glaucoma valve, may lead to satisfactory results, but fibrosis represents a
72 common complication that reduces their success rate. Ponnusamy et al [19] have designed
73 and manufactured porous mitomycin C (MMC) and 5-fluorouracil (5-FU) releasing thin films
74 of PLGA, using a spin-coating technique. The double-layered biodegradable films provided a
75 continuous release of antifibrotic drugs for a period of 28 days and may be used as coating
76 for GDD implants.

77

78 **3. DIAGNOSTICS**

79 Optical coherence tomography (OCT) is a valuable tool that allows diagnosis and monitoring
80 of a number of ophthalmic diseases, such as AMD, diabetic retinopathy and glaucoma. The
81 growing impact of OCT on management of ocular diseases underlines the necessity of
82 standardized assessment of OCT devices. According to Baxi et al [20], thin films may
83 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.

4. 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.

5. 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

127 fabricated PLGA thin films that were loaded with rapamycin and were developed on the
128 surface of IOLS. In vivo experiments demonstrated satisfactory anti-inflammatory and anti-
129 proliferative results.

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131 6. RETINAL SCAFFOLDS

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

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

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

159

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

168

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

were non-porous, 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 manufactured thin films from poly (hydroxybutyrate-co-hydroxyvalerate) (PHBV) in order to culture RPE cells. [44] 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 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. [45]

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]

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.

230 **ETHICAL ISSUE**

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232 There are no ethical issues in this review.

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