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Protocols

Restructuration kinetics of amphiphilic intraocular lenses during aging

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ABSTRACT

Photooxidation and hydrolysis are the two primary aging factors of intraocular lenses. Opacifications, dislocations, glistening and yellowing of the implanted acrylic lenses, which are due to chain scissions and depolymerization, are the consequences of aging from the clinical perspective. The purpose of this study was to examine the consequence of the aging of intraocular lenses on chemical and surface properties. Acrylic lenses made of poly acrylic-co-polystyrene polymer were artificially aged by photooxidation and hydrolysis from 2 to 20 years. Degradation products were observed by Reverse-phase High-Performance Liquid Chromatography RP-HPLC and thermogravimetric analysis (TGA). The surface, which was analyzed by atomic force microscopy (AFM) and fibronectin adhesion kinetics, was chosen as an indicator of intraocular biocompatibility. Low-molecular-weight degradation products (LMWP) result from chain scission under both hydrolysis and photooxidation. The osmotic effects of water enable degradation products to migrate through the polymer. A portion of the degradation products exudate in the surrounding center, whereas a portion link with lateral chains of the polymer. At the same time, the surface roughness evolves to externalize the most hydrophilic chains. As a result, the fibronectin adhesion level decrease with time, which indicates the existence of a biocompatible kinetic for implanted intraocular lenses.

1. Introduction

Constant oxidative attack by inflammatory cells is one of the primary *in vivo* degradation factors that can alter the biocompatibility of polymers and compromise the function of implants. Degradation also stems from thermal degradation, ozone-induced degradation, mechanochemical degradation, catalytic degradation and biodegradation with multiple consequences. Degradation can also generate new chemicals that increase oxidative stress [1]. For acrylic copolymers, hindsight provides useful information regarding natural aging and artificial aging [2]. For example, the presence of unsaturated functions on the carbon chains explains the color evolution of the polymer, which is often characterized by yellowing [2]. Regardless of the structure, the mechanisms of degradation remain mostly comparable [3].

Holland et al. and others have described Poly (methyl methacrylate) (PMMA) thermal degradation in 3 steps. The first step occurs between 150 °C and 200 °C, which relates to the degradation of hydrogen bonds. The second step pertains to the cleavage of unsaturated bonds, which is located at the end of the polymer chains, as per the other two steps. The process includes the radical transfer of vinyl function and, afterwards, the function of the chain. The third PMMA degradation step corresponds to β-cleavage and random cleavage of the polymer alkyl chains [4,5]. For polyacrylates, exposure to light in the presence of oxygen can result in the cleavage of the chains with or without recombination, polymerization and cross-linking reactions. Whatever the involved degradation mechanism may be, it seems that the degradation products formed are the same [6].

When entering the composition of implantable medical devices, the aging of polymeric materials may result in clinical symptoms. Intraocular lenses can lose their transparency or be dislocated during their aging process [7,8]. Swelling and glistening phenomenon have been described for polyacrylic lenses. The change in the reflection of these lenses resulted from the formation of small aqueous

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vacuoles inside the hydrophobic material which, because the eye temperature exceeds the copolymer Tg, may migrate to other parts of the matrix and generate smaller vacuoles [9–13]. Glistening can affect the light transmission properties and hence alter visual acuity in the dark [14–16]. Lens dislocation is a more marginal complication that is sometimes observed in cases of inflammatory intraocular pathologies, such as uveitis or pseudoexofoliation syndromes [7,17].

Regarding the scientific and medical literature, there must be a link between the aging of polyacrylate lenses and intraocular biocompatibility. The posterior capsular opacity is the most described and studied biocompatibility issue in the lens extraction surgery procedure.

To date, intraocular lenses and surgery have remained the only effective treatment for cataracts, but often complications, such as posterior capsular opacity (PCO), have been observed [18,19], due to the migration and proliferation of the remaining lens epithelial cells (LECs) on the capsule, through the visual axis. In the patient carrying an intraocular lens (IOL), LEC migration occurs between the posterior space of the capsule and the implant's surface.

PCO does not affect the patients in the same way, owing to their individual characteristics and the kind of implant used [20,21]. According to Linnola et al., the protein adhesion on the implants and on the capsule is a key element towards the biocompatibility of the lens implant per the "sandwich theory." Fibronectin is adsorbed on both the implant and the capsule, thereby promoting their adherence and forming a barrier against cell proliferation over the capsule. Fibronectin adhesion occurs quickly, within several minutes or several hours after surgery [22–24].

PCO can occur up to 15–20 years after surgery, even after the implant removal. Hitherto, these late PCO have not been fully explained. PCO physiopathology can occur over a long period where both the implant and lens capsule may be involved. Some preventive methods have reduced the occurrence of this complication, but it is not entirely eradicated [21]. Late PCO has been correlated with the loss of the barrier effect of the square edge of the implant [25]. This loss seems to have more to do with a change in the chemical composition of the lens, particularly after aging, rather than to the lens design [26–29]. The surface properties of the lens could also be responsible for the late onset of PCO [30,31].

Specific surgical procedures [21,32–34] or post-surgical medications based on steroids, for instance [35], have been used to anticipate PCO occurrence. Beyond those procedures, the importance of the adherence process as a preventive measure between the implant and the capsule has made the lens design one of the major topics in surgery. All meta-analyses have concluded that there is a benefit of one-piece of implant made of hydrophobic acrylate copolymers and designed with square edges [32,34,36–38]. Nishi et al. has even inferred that the lens design alone may impact the PCO rate. The copolymer composition of the lens has been designed to prevent PCO after cataract surgery [39]. Nevertheless, so far, *in vitro* and *in vivo* studies have proved that protein adhesion and biocompatibility are more related to the implant surface properties than to the lens design itself [40–43]. Some authors have tested the effect of surface pegylation (PEG) on the PCO rate. The effects of PEG depend on the copolymer properties and the pegylation procedure [44–46]. The results differ according to the authors, but the PEG grafting on the lens surface seems to be the most efficient design prevention to avoid PCO [47–50]. EnVISTA® is an implant made on the hydrophobic acrylate, hydrophilic acrylate and styrene. An intraocular lens manufacturer has developed a hydrophobic implant with 4% water, while most of the hydrophobic implants contain less than 1%. Unlike the pure hydrophobic implants, this copolymer is supposed to have no glistening formation. The copolymer's chemical structure involves PEG sequences on the lateral chains of the acrylate copolymer bone that are supposed to help with protein adhesion and limit the appearance of PCO [10,14,51].

Table 1
IOLs aging groups.

Name	Hydrolysis	Temperature	Xenon-arc
Simple hydrolysis	YES	34 °C	–
Forced Hydrolysis	YES	70 °C	–
Photooxidation	–	34 °C	YES 9.6 h
Combined photooxidation	YES	34 °C	YES from 9.6 (short), 96 (long) to 960 h

Considering these results, we hypothesized that the late appearance of PCO is the consequence of protein biding modification between the eye and the capsule that result in changes to the physical and chemical surface within the aging lens. To make that point, we developed a transversal analysis of the copolymer before and after aging, which give answers regarding the thermic properties, degradation, release of degradation products and the consequence on protein sorption on the surface.

2. Materials and methods

2.1. Implants and monomers

EnVISTA® amphiphilic implants were purchased from Bausch & Lomb (Bridgewater, New Jersey, USA). All of the implants had the same design, diopter (+20D) and batch number. The implants were all preserved at room temperature (+20 °C) in the original sterile packaging for less than 3 months until use.

The following acrylic monomers were used: ethylene glycol phenyl ether acrylate (EGPEA), 2-hydroxyethyl methacrylate (HEMA), ethylene glycol dimethacrylate (EGDM) and styrene. They were purchased from Sigma Aldrich (Saint Louis, Missouri, USA).

2.2. Aging procedures

Three aging factors were applied: hydrolysis, heating and photooxidation under artificial light.

The solvent for hydrolysis was sterile saline solution (NaCl 0.9%), which simulate aqueous humor. Temperature was set by the oven without any light exposure. Two temperatures were chosen. The first was the physiological eye temperature (34 °C) (Kato, 2001). The second (70 °C) was chosen way above the glass transition temperature (Tg) of the enVISTA® copolymer (28 °C) [14].

A Qsun Xe-1 xenon arc chamber was used to reproduce solar exposure in lab conditions (Labomat Essor, Saint-Denis, FRANCE). The artificial sunlight irradiation power was set at 6.8 mW/cm^2 and ranged from 300 to 400 nm. According to Labomat Essor data and international standard organization (ISO 11979-5), 96 h of xenon arc exposure may reproduce to 2 years of aging by natural sunlight. All procedures are summed up in Table 1.

Each sample was washed before and after the aging procedure. One milliliter of deionized water was used to eliminate all saline deposits on the surface of the implant. After aging, the implants were stored in dry and dark conditions at room temperature.

2.3. Aged solutions analyses

The washing solutions, the aged solutions and the conservative solutions were all analyzed by the RP-HPLC method developed for the detection of acrylic monomers and acrylic degradation products [52].

The HPLC system is a Dionex-ThermoFisher Scientific ultimate 3000 HPLC that is equipped with an LPG-3400SD pump, WPS-