Experimental study of the mechanisms leading to the formation of glistenings in intraocular lenses by Raman spectroscopy

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Abstract: The phenomenon of glistenings, often appearing in intraocular lenses (IOLs) of patients after some time from the surgical operation, is potentially able to induce a poor quality of vision and, therefore, frustrate IOL implantation itself. In this paper, we combine optical microscopy with micro-Raman spectroscopy to get a deeper insight on the mechanism ruling, at microscopic scale, glistening formation. In particular, we have analyzed two types of IOLs, characterized by a different internal hydrophobicity but a similar polymer hydration coefficient. Raman imaging of single microvacuoles reveals that water creeps into the polymeric network, which traps water. Finally, applying the Principal Component Analysis (PCA) to Raman data, we provide information on the probable mechanism leading to water trapping in the two kinds of analyzed IOLs.

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1. Introduction

An intraocular lens (IOL) is an artificial lens used to replace the eye’s natural crystalline lens, when it is affected by cataract or other degenerative processes rendering it opaque [1]. It is estimated that around 20 million surgical operations per year are practiced worldwide, a level that will surely increase in view of the extension of the average life.

The materials employed for IOLs have been evolving since the pioneering demonstration by Harold Ridley in 1949 [2]. The polymethylmethacrylate – PMMA – (commonly called Plexiglass) was originally chosen because of its high transparency and the excellent biocompatibility. However, the rigidity of PMMA required quite large surgical incisions, which increase post-operation risks and hospitalization time. Within this scenario, new flexible polymer materials have been introduced to satisfy high levels of biocompatibility and optical functions and, mostly, to squeeze the IOL in order to introduce it in the eye through the smallest possible incision (2-3 mm against 5-7 mm for rigid materials). A first significant progress to this goal came with the introduction of silicone-based IOLs [3] and, later, hydrogel lenses [4,5]. Hydrogels IOLs are formed by poly-hydroxyethyl methacrylate - poly-HEMA, a cross-linked polymer, which is rigid in absence of water but that swells in water, assuming the consistence of a foldable gel. Nowadays, the rise of foldable lenses has led to the development of a wide spread versions of flexible hydrophobic IOLs on the market. These materials are formed by copolymers, i.e. a mixing of monomers of methmethacrylate (MMA), ethylmethacrylate (EMA), 2-hydroxyethyl methacrylate (HEMA), etc. By varying several parameters, such as the flexibility of side chains substituents and the amount of the single monomers and cross-linking between polymer chains, different types of hydrophobic acrylic co-polymers can be produced exhibiting different chemico-physical properties. For example, PMMA provides the rigidity of the material while the presence of the PEMA gives a
certain elasticity and rubberiness [6–8]. Moreover, the hydroxyl group in poly-HEMA is responsible of the increasing of the polymer's hygroscopy [9].

Water capture is a problem that affects, with varying intensity, all the IOL materials. Hydrophilic polymers, at equilibrium, have water content of 18-32%, while hydrophobic materials only 0.1-0.5% [9]. Usually, water diffuses into the IOL material and can reach lower density areas, which behave as cavities. When water is uniformly dispersed within the lens (i.e. the cavities are extremely fine) it does not lead to vision problems. Differently, when the water is segregated in localized microscopic areas, it gives rise to the formation of water micro-droplets. This phenomenon, called “glistenings”, can lead to problems to the vision. In fact, an anomalous concentration of water in some areas causes refractive index jumps and, therefore a diffusion of the light rays that can alter the image quality on the retina. However, the effective impact of glistenings on vision is still a matter of debate in literature, being the vision capability a combination of optical and neural function [10–13]. Glistenings occurs after a certain time after the implantation, ranging from several months up to a few years [14]. At the slit lamp examination, the IOL shows a glistenings caused by the scattering from water inclusions (microvacuoles), not observable before implantation [15]. When the size and the number of these defects exceed a certain threshold the vision quality of the patient can be significantly compromised [16].

Glistenings was first observed in hydrophobic acrylic IOLs but it was also verified in other IOL materials, including silicone, hydrogel and poly(methyl methacrylate). Under an optical microscope, glistenings are usually distributed throughout the entire IOL. They consist of a myriad of small microvacuoles whose shape can be spherical but, more frequently, ellipsoidal, whose size vary between a few μm up to 10 μm. Larger sizes (even more than 20 μm) may be observed during in vitro studies in which glistenings is induced by thermal shock. Typically, glistenings tends to disappear when IOLs are removed from water and dried. Interestingly, upon subsequent hydration, in many cases, the glistenings tend to reappear and grow in the same positions. Extensive studies have been devoted to physical parameters of glistenings (scattering, and transmittance) [17–20] and on their effect on the vision (contrast sensitivity and visual acuity) [21–26].

Multiple studies have evaluated the possible mechanism of glistenings formation within IOLs [27–37]. Spinodal decomposition is a mechanism, which certainly takes place in the IOL’s material. The initial homogeneously miscible multi-component polymeric network separates into different immiscible domains caused by thermal stress. Kato et al.’s [37] describe this phenomenon in AcrySof IOL using thermodynamics parameters. Moreover, they also claim that micro-vacuoles are localized in the same positions when the material is undergone to successive heating-cooling processes [37].

According to a more recent theory [27] cavities development is attributed to osmotic pressure differences between the cavity and the liquid in which IOL is embedded. Following these conjectures, glistenings formation is the result of hydrophilic impurities initially present as second-phase particles [28–31] or generated by hydrolysis during aging [32].

So far, all the studies based on physical techniques have focused on macroscopic optical effects (scattering, transmission) or, on mechanisms and modeling of cavity growth. No studies have been carried out on a molecular basis of the phenomenon, i.e. on the chemical nature of the polymer and the changes induced by glistenings. This work is aimed to demonstrate that Raman spectroscopy (RS) can represent a very powerful tool to explore the intriguing mechanism of glistenings formation.

Raman spectroscopy is a well-consolidated analytical spectroscopic technique [38] widely employed in many fields of the research, as life sciences [39,40], soft matter [41] and polymer science [42]. Indeed, the high chemical specificity of RS allows identifying the species forming the sample under investigation and their concentrations. Finally, combining RS with optical microscopy, Raman spectra can be acquired at micrometric scale (micro-Raman), and Raman maps of selected chemical components can be easily obtained [43].
Raman spectroscopy has been already used to study systems of ophthalmological interest [44,45] and also to characterize contact lenses and human lenses [46–51]. In this work we combine optical microscopy with micro-Raman spectroscopy to analyze limited portions of the IOL around a single microvacuole. In particular, we compare two different IOL materials: the first is a common hydrophobic acrylate copolymer, while the second one differs for the presence of a certain amount of hydrophilic polymer component. We performed an accurate analysis of the intensity of the polymer and water bands getting information on how water is dispersed in the microvacuole. In addition, using a multivariate statistical analysis (Principal Component Analysis, PCA) we shed light on the confinement of water in the microvacuole.

2. Materials and methods

2.1 IOLs

We have performed both optical and Raman analysis on two types of copolymers-based IOLs, provided by Soleko s.p.a. The first type of IOLs, referred in the following as HFO (Hydrophobic Foldable Ocular) lenses, is known to exhibit a significant level of glistenings. The polymer blend for HFO includes (see Fig. 1): Alkyl (meth)acrylates, Alkoxyalkyl (meth)acrylate, Phenylalkyl (meth)acrylate and some crosslinkers as f-((meth)acryloyloxy)alkyl (meth)acylates and Bis-g-g-((meth)acryloyloxy) alkyl)alkyl(meth)acrylates. For the second type of IOLs, herein referred as A-HFO (Advanced-Hydrophobic Foldable Ocular) lenses, the polymer blend was modified replacing Alkyl (meth)acrylates with Hydroxyalkyl (meth)acrylates (see Fig. 1). The presence of this latter reduces the internal hydrophobicity of the material without increasing the hydration coefficient of the polymer, which remains around 1%. For both IOL types, both an UV-blocking polymer (Benzotriazol phenol) and a radical initiator (Bis-alkyl peroxydicarbonates) were added to the polymer blends. Both materials have a glass transition temperature well below the physiological temperature: 12 °C for HFO and 8 °C for A-HFO. The refractive index of the investigated IOLs types are: 1.526 (@546 nm, T = 20 °C) and 1.506 (@546 nm, T = 20 °C) for HFO and A-HFO, respectively. At equilibrium in water solutions, water content was of 1.1% (HFO) and 2.9% (A-HFO). Typical optical power of the analyzed IOLs was ≈20 dioptries.

![Fig. 1. Chemical structure of the monomers forming the copolymers of IOLs here investigated.](image-url)
2.2 Glistenings activation

Glistenings was activated following the protocol explained in ref [52]. In brief, IOL was kept in a distilled water bath at 48 °C for 48 hours. During this time the water permeates IOLs, which, however, remain still transparent. Afterwards, a thermal shock was applied by immersing quickly the IOLs in a second distilled water bath at 25°C and kept for 24 h. The activation protocol and the optical images of the IOLs are depicted in Fig. 2a while in part b we show typical images of HFO and A-HFO lenses as they appeared at the end of the process.

![Fig. 2. (a) Cartoon of the procedure for glistenings activation. (b) Typical optical images of IOL after glistenings activation: upper HFO, lower A-HFO. The bar scale is of 30 μm.](image)

2.3 Raman system

Raman spectra were acquired with an inverted Raman confocal microscope (WiTec, Alpha 300). The system is equipped by an excitation laser source at 532 nm. The laser was focused on the IOL through a 60x microscope objective (NA = 0.8). The backscattered light, collected with the same objective lens, was filtered by an edge-filter and guided to the spectrograph by a 50-μm core optical fiber, which assures also system confocality. The Raman photons, dispersed using a 600 lines/mm grating, were recorded by a CCD detector cooled at −60°C. The spatial resolution of our confocal system, was estimated to be ~0.6 μm in the transverse plane and ~1.4 μm along the longitudinal axis. After glistenings induction, IOLs were quickly fixed to the glass bottom of a Petri dish. Therefore, in order to avoid IOLs drying, the dish was filled by distilled water. Typically, the Raman beam power impinging on the sample was 6 mW and the integration time for each spectrum was 1 s. In these conditions, signal fluctuations lower than one part in 10^3 were observed, as estimated by repeated acquisitions of the Raman signal on the same point. Spectra were collected in the 250-4000 cm⁻¹ region, with a spectral resolution of ≈3 cm⁻¹.

3. Results and discussion

3.1 Optical analysis of glistenings

Once reached the equilibrium condition, both IOLs were preliminarily observed with an optical microscope in order to evaluate the glistenings extent. As expected, the field of view was crowded by a huge number of microvacuoles for HFO whose size ranged from 5 to 25 μm. On the contrary, A-HFO exhibited a much lower number of microvacuoles, mainly consisting of tiny particles and often the whole field of view of the microscopes appeared completely free from microvacuoles. Importantly, due to the extremely low number of vacuoles, we can consider A-HFO lenses with a glistening grade = 0, according to the Miyata grading system [33]. The analysis of the vacuoles for HFO lenses, in terms of the number of vacuoles and their size, was performed by acquiring the IOLs images within a 160 μm x 130
μm window at different depths \( h \) in the material (\( h = 20, 100, 180, 260 \) and \( 340 \) μm). As can be seen in Fig. 3a, only a few vacuoles show a spherical shape, while most of them appear to be ellipsoidal. This is reasonably related with the random dynamics of the process of co-polymerization, which leads to an inhomogeneous structure. As a matter of facts, the bulk polymer net is not completely connected, and the polymer chains are not perfectly folded. As a consequence, lower density regions can be randomly formed, which are prone to be filled with water. On the other hand, water filling of such cavities results in a refraction index jump, giving rise to light scattering. In order to calculate the size distribution of the microvacuoles, we estimated the ellipsis area by measuring the axes \( a \) and \( b \) (see Fig. 3a). Figure 3b shows the distribution of the areas of the ellipses at different penetration depths in the IOL, together with the respective mean values and standard deviations. The largest vacuoles were observed in the inner lens region, an outcome clearly related to the difficulty of water to be expelled from the lens during the shrinking induced by the thermal shock. Consistently with this, vacuole areas start to decrease for \( h \) values approaching the upper edge of the IOLs. Finally, Fig. 3c shows the behavior of the number of vacuoles (found in an area of \( 0.02 \) μm²) and the average areas of the vacuoles versus the penetration depth in the IOL.

Fig. 3. (a) Optical images of HFO lens. The two inserts show a magnification of a typical spherical and ellipsoidal vacuole. (b) Area distribution of the ellipses calculated at three penetration depth in the IOL (\( h = 20, 100 \) and \( 180 \) μm). Average area and standard deviation are reported for each histogram. (c) Behavior of the total number of vacuoles found in an area of \( 0.02 \) μm² (upper part) and of the average area (lower part) versus the penetration depth in the IOL.
3.2 Raman spectra of IOLs

As a first step, we recorded the Raman spectra of the IOLs before glistenings induction. In Fig. 4 we show the spectra of HFO and A-HFO in the frequency range from 500 to 3800 cm\(^{-1}\). A first, important information provided by these spectra relies on IOL material biocompatibility. As a matter of facts, a crucial issue for polymeric materials biocompatibility is the presence of monomers not completely polymerized [48]. Interestingly, such monomers exhibit strong Raman bands, which disappear after polymerization. This is the case of the band at 1640 cm\(^{-1}\), assigned to the C = C bond (stretching mode), so that this band can be used as sensitive probe to monitor the presence of residual monomers. Since this peak is completely absent in our spectra this denotes a quite good degree of biocompatibility of the analyzed materials. Most of the observed Raman bands of HFO lenses are identified with those reported in the literature [53–62]. The bands in the range 800 - 1800 cm\(^{-1}\), i.e. 496, 622, 768, 1004, 1032, 1157, 1181, 1204, 1346, 1449, 1585, and 1605 cm\(^{-1}\), can mainly ascribed to ring vibrations and to alkyl groups. Other bands, as the band at 1730 and 1460 cm\(^{-1}\), are attributable to \(\nu(C = O)\) of C-COO and \(\delta(C-H)\) of O-CH\(_3\), respectively. The wide band between 2600 and 3200 cm\(^{-1}\) results from the convolution of many symmetrical and asymmetrical stretching vibrations of CH\(_{2,3}\) bonds. Finally, for HFO lenses, it is worth noticing the presence of a small, but detectable peak around 3540 cm\(^{-1}\) (see figure inset). This band is ascribable to free hydroxyl groups and can be clearly distinguished by the much broader OH stretching bands in water molecule (O-H symmetric and asymmetric stretching modes in the 3200-3700 cm\(^{-1}\)) [63].

![Fig. 4. Typical Raman spectrum acquired in a HFO (i) and in a A-HFO (ii) IOL.](image)

3.3 Raman analysis of single microvacuoles

Measurements were performed by acquiring the Raman spectra in a raster scan centered on a single isolated microvacuole in the vacuole equatorial plane. The selected windows were chosen slightly larger than the size of the vacuole, in order to probe also the polymer around the vacuole. Typically, raster scans were performed on 20 \(\mu\)m x 20 \(\mu\)m regions, with a step of 0.5 \(\mu\)m. The Raman beam power impinging on the sample was 6 mW and the integration time for each spectrum was 1 s. This procedure was followed for both types of IOL analyzed in this study.
3.3a Raman analysis of glistenings in HFO

Figure 5, part a, shows the typical Raman spectra recorded externally (i) and internally (ii) to the microvacuole shown in the inset of the same figure. As it can immediately noticed, both spectra reproduce the spectrum acquired before glistening induction (Fig. 4) except for the spectral region 3200–3700 cm\(^{-1}\) where new peaks appear. In particular, inside the vacuole it is possible to note the co-presence of the water bands (symmetric and asymmetric OH stretching) and polymer bands. Clearly, the intensity of the polymer bands is weaker than the external part. This can be immediately understood because inside the vacuole the polymer concentration decreases in favor of water. Globally, these outcomes suggest that vacuoles are not simply water-filled cavities but are rather regions in which, in some way, a co-presence of polymers and water occurs. In order to estimate the mean water concentration inside the microvacuole we normalized the polymer and water intensity bands to those obtained with pure sample of the two components. By calculating the average values of polymer and water bands inside the microvacuole we found a relative water concentration of 23%. Vice versa, externally to the vacuole, the water band is not appreciable, at least at the levels of our sensitivity. Nevertheless, we observed the presence of the previously mentioned OH band, as highlighted in the inset of Fig. 5a. The presence of the OH-free peak, observed only after glistenings induction, can be reasonably ascribed to hydrolysis processes of ester groups, accelerated by the protocol used to induce glistenings (high temperature followed by thermal shock). The slightly reduced polymer concentration inside the vacuole can be used to create a Raman image of the vacuole, by plotting in a color scale the intensity band (area) of the polymer band in the region 2800 - 2900 cm\(^{-1}\) (see Fig. 5b). A similar image can be obtained by plotting the intensity of the water band in the range 3200 - 3700 cm\(^{-1}\). As it can be noticed, despite of the contemporary presence of water (inside) and free OH (outside) the vacuole, the difference between these two bands is able to create a contrast sufficient to reproduce the vacuole (Fig. 5c). A deeper insight on the mechanism ruling glistenings formation can be obtained by a multivariate spectra analysis. In particular, we performed Principal Component Analysis of spectra acquired in the previously mentioned raster scan. Figure 5e and 5f reproduce the score maps for the first and second PCs, respectively, while Fig. 5d shows the PC loadings related to both PCs. Interestingly, PC1 score map is quite similar to the simple Raman maps of Fig. 4b,c, reproducing the vacuole shape. High score values correspond to points with a high polymer component (positive loading features) while low score values correspond to points with a high water content (negative loading components). Therefore, globally PC1 map and loading summarizes the information of both 5b and 5c maps. More intriguing is the outcome provided by PC2. As a matter of facts, PC2 score map defines the microvacuole border, suggesting the presence of a reduced hydration shell around the vacuole. Moreover, it is possible to reveal in the loading the counter-variation of polymer Raman features, with negative CH\(_{2,3}\) bands and the positive 1001 cm\(^{-1}\) peak. This latter can be ascribed to vibrations of the phenyl group, therefore suggesting an enhanced presence of these moieties in the region around the vacuole. Given the hydrophobicity of the phenyl rings, it is reasonable to speculate that this creates a “cage” for water molecules, which, feeling an unfavorable hydrophobic environment, are forced to remain confined in a more hydrophilic region, giving rise to the microvacuole. In this frame, microvacuoles would be generated by the somewhat casual arrangement of the polymeric components in the complex IOL texture.
Fig. 5. (a) Typical Raman spectra obtained in a point external (i) and internal (ii) at the microvacuole. The inset shows an optical image of the microvacuole selected for Raman analysis in HFO. The dashed borders delimit the region scanned by the laser. (b) Raman image of the microvacuole shown in part a), obtained selecting the polymer band intensity (area) between 2800 and 2900 cm$^{-1}$. (c) Water distribution inside the vacuole obtained by plotting the intensity of features between 3200 and 3700 cm$^{-1}$. (d) Loading plot for the first (bottom) and second (upper) PC, resulting from the analysis of spectra acquired in a raster scan around the vacuole. (e) PC1 score map from PCA of Raman spectra. (f) Same as in e), but for the second PC.

3.3b Raman analysis of glistenings in A-HFO

An analysis similar to that performed for HFO was repeated for A-HFO. As mentioned in the Section 2.1, for this type of IOL glistenings was much more rarified and, on average, microvacuoles tend to be much smaller. We again selected one microvacuole and analyzed a region around it. Typical Raman spectra registered outside and inside the microvacuole are reported in Fig. 6a. Similarly to the case of HFO, the spectrum recorded inside the microvacuole exhibited the typical broad O-H stretching band of water between 3200 and 3700 cm$^{-1}$, while outside the vacuole water bands are replaced by the narrower O-H free peak, also observed before glistening induction. So, in order to estimate the effective water concentration inside the microvacuole, we subtracted the OH-free found for dry IOL. The water concentration inside the microvacuole for A-HFO was found of 18%, against the 23% found for HFO. Similar concentration values were found for numerous vacuoles analyzed in this study, confirming the much lower tendency of water to be confined in a micro-sized region. Raman imaging of the selected microvacuole, obtained both in terms of Raman band intensity (Fig. 6b and Fig. 6c) and in term of PC1 score maps (Fig. 6e), provide similar information obtained for the HFO case, reproducing nicely the vacuole geometry. Nevertheless, somewhat different can be revealed by PC2 analysis. Indeed, although PC2 highlights variation associated to the distribution of the hydrophobic phenyl rings (see negative features of PC2 loading at 1001, 1204 and 1401 cm$^{-1}$), PC2 scores spatial distribution only partially reproduces the hydrophobic cage observed for the HFO case. As a
matter of facts, it is reasonable to speculate that, in this case, the presence of a well-distributed hydrophilic component, water is prone to be spread over the whole IOL polymeric matrix, hence avoiding trapping by phenyl ring rich environments.

![Image](image_url)

**Fig. 6.** (a) Typical Raman spectra obtained in a point external (i) and internal (ii) at the microvacuole. The inset shows an optical image of the microvacuole selected for Raman analysis in A-HFO. The dashed borders delimit the region scanned by the laser. (b) Raman image of the microvacuole shown in part a), obtained selecting the polymer band intensity (area) between 2800 and 2900 cm$^{-1}$. (c) Water distribution inside the vacuole obtained by plotting the intensity of features between 3200 and 3700 cm$^{-1}$. (d) Loading plot for the first (bottom) and second (upper) PC, resulting from the analysis of spectra acquired in a raster scan around the vacuole. (e) PC1 score map from PCA of Raman spectra. (f) Same as in e), but for the second PC.

### 4. Conclusions

The materials that make up intra ocular lenses are quite complex, result of chemically and physically connected polymer chains. The process of co-polymerization, intrinsically random, gives place to a heterogeneous and not completely connected bulk polymer. As a consequence, regions with lower density can appear, which can be prone to be filled with water that originate the phenomenon of glistenings. In this work we have investigated two types of IOLs, characterized by materials with a different degree of hydrophobicity, which gives rise to a quite different glistenings manifestation. We started with a conventional optical microscopy analysis from which we found that microvacuoles tend to be accumulated in the innermost part of the IOL, where they also reach the largest size. While the glistenings is quite evident in HFO lens, in the case of A-HFO the number of microvacuoles is essentially negligible (glistenings grade 0). In the second part of our study we focused on single microvacuoles by means of Raman spectroscopy. By analyzing the polymer and water Raman bands, we have noticed that vacuoles are not water-filled pockets but rather spatial regions in which water coexists with the polymeric network. We also quantitatively estimated the water concentration inside a microvacuole: 23% for HFO against 18% for A-HFO. Moreover, by
performing PCA of Raman spectra, we observed an enhanced presence of phenyl ring moieties around the vacuole. Given the hydrophobicity of these latter, it is reasonable to speculate that this arrangement creates a cage for water molecules, which, feeling an unfavorable hydrophobic environment, are forced to remain confined in a more hydrophilic region, giving rise to the microvacuole. The cage effect is quite reduced for glistenings in the more hydrophilic IOL, reasonably because in presence of a well-distributed hydrophilic component, water is prone to be spread over the whole IOL polymeric matrix, therefore avoiding trapping by phenyl rings rich environments. Clearly, it is possible that other monomers contribute to the material hydrophobicity, ruling therefore the glistenings formation in other hydrophobic IOLs materials. In conclusion, we have observed that thanks to a well-balanced mixing of hydrophobic and hydrophilic polymers, glistenings can be eliminated. Indeed, while for HFO lens water, once penetrated in the polymer, seems to be collected in vacancies, for A-HFO water is better dispersed throughout the material. Notably, the experimental approach shown in this paper could be used in the next future to include other clinically available hydrophobic acrylic IOL materials.

Acknowledgments

The authors thank Soleko s.p.a. for supplying of IOLs used in our experiments and, in particular, Dr. M. Conte, Dr. A. Quercioli and G. Carnacina for the stimulating discussions on the composition of the polymer compounds. Authors thank also Prof. O. Tarallo for the fruitful discussions on polymer chemistry.

Disclosures

The authors declare that there are no conflicts of interest related to this article.

References

1. D. V. Leaming, “Practice styles and preferences of ASCRS members–1994 survey,” J. Cataract Refract. Surg. 21(4), 378–385 (1995).
2. H. Ridley, “Intra-ocular acrylic lenses; a recent development in the surgery of cataract,” Br. J. Ophthalmol. 36(3), 113–122 (1952).
3. K. R. Mehta, S. N. Sathe, and S. D. Karyekar, “The new soft intraocular lens implant,” J. Am. Intraocul. Implant Soc. 4(4), 200–205 (1978).
4. E. Epstein, “History of intraocular lens implant surgery,” in Soft implant lenses in cataract surgery, T. R. Mazzocco, G. M. Rajacich, E. Epstein, ed. (Slack, 1986).
5. R. Menapace, M. Ammon, and U. Radax, “Evaluation of 200 consecutive IOGEL 1103 capsular-bag lenses implanted through a small incision,” J. Cataract Refract. Surg. 18(3), 252–264 (1992).
6. L. Werner, D. J. Apple, M. Escobar-Gomez, A. Ohström, B. B. Crayford, R. Bianchi, and S. K. Pandey, “Postoperative deposition of calcium on the surfaces of a hydrogel intraocular lens,” Ophthalmology 107(12), 2179–2185 (2000).
7. E. J. Hollick, D. J. Spalton, P. G. Ursell, and M. V. Pande, “Biocompatibility of poly(methyl methacrylate), silicone, and AcrySof intraocular lenses: randomized comparison of the cellular reaction on the anterior lens surface,” J. Cataract Refract. Surg. 24(3), 361–366 (1998).
8. E. Epstein, “Use of soft lenses,” J. Cataract Refract. Surg. 16(6), 779 (1990).
9. M. Tetz and M. R. Jorgensen, “New hydrophobic IOL materials and understanding the science of glistenings,” Curr. Eye Res. 40(10), 969–981 (2015).
10. D. B. Elliott, “Contrast sensitivity decline with ageing: a neural or optical phenomenon?” J. Cataract Refract. Surg. 4(5), 415–419 (1987).
11. L. Werner, J. C. Stover, J. Schwiegerling, and K. K. Das, “Effects of Intraocular Lens Opacification on Light Scatter, Stray Light, and Overall Optical Quality/Performance,” Invest. Ophthalmol. Vis. Sci. 57(7), 3239–3247 (2016).
12. K. K. Das, J. C. Stover, J. Schwiegerling, and M. Karakelle, “Technique for measuring forward light scatter in intraocular lenses,” J. Cataract Refract. Surg. 39(5), 770–778 (2013).
13. H. Nishihara, S. Yaguchi, T. Onishi, M. Chida, and M. Ayaki, “Surface scattering in implanted hydrophobic intraocular lenses,” J. Cataract Refract. Surg. 29(7), 1385–1388 (2003).
14. D. K. Dhaliwal, N. Mamalis, R. J. Olson, A. S. Crandall, P. Zimmerman, O. C. Alldredge, F. J. Durcan, and O. Omar, “Visual significance of glistenings seen in the AcrySof intraocular lens,” J. Cataract Refract. Surg. 22(4), 452–457 (1996).
15. D. Tripti, R. S. Haldar, S. Geetha, K. Niyogi, and R. K. Khandal, “Materials for intraocular lenses (IOLs): Review of developments to achieve biocompatibility,” E-Polymers 9(1), 124 (2009).
16. U. Gunenc, F. H. Oner, S. Tongal, and M. Ferfiehl, “Effects on visual function of glistenings and folding marks in AcrySof intraocular lenses,” J. Cataract Refract. Surg. 27(10), 1611–1614 (2001).
17. D. H. Kim, R. H. James, R. J. Landry, D. Calogero, J. Anderson, and I. K. Ilev, “Quantification of glistenings in intraocular lenses using a ballistic-photon removing integrating-sphere method,” Appl. Opt. 50(35), 6461–6467 (2011).
18. J. M. Artigas, A. Felipe, A. Navea, M. C. García-Domene, Á. Pons, and J. Mataix, “Determination of scattering in intraocular lenses by spectrophotometric measurements,” J. Biomed. Opt. 19(12), 127006 (2014).
19. B. N. Walker, R. H. James, D. Calogero, and I. K. Ilev, “A novel full-angle scanning light scattering profiler to quantitatively evaluate forward and backward light scattering from intraocular lenses,” Rev. Sci. Instrum. 86(9), 095004 (2015).
20. T. Oshika, Y. Shiokawa, S. Amano, and K. Mitomo, “Influence of glistenings on the optical quality of acrylic foldable intraocular lens,” Br. J. Ophthalmol. 85(9), 1034–1037 (2001).
21. S. Yoshida, H. Matsushima, M. Nagata, T. Senoo, I. Ota, and K. Miyake, “Decreased visual function due to high-level light scattering in a hydrophobic acrylic intraocular lens,” Jpn. J. Ophthalmol. 55(1), 62–66 (2011).
22. A. Waite, N. Faulkner, and R. J. Olson, “Glistenings in the single-piece, hydrophobic, acrylic intraocular lenses,” Am. J. Ophthalmol. 144(1), 143–144 (2007).
23. H. Minami, K. Toru, K. Hiroi, and S. Kazama, “Glistenings of Acrylic Intraocular Lenses,” Rinsho Ganka 53(5), 991–994 (1999).
24. J. Colin and I. Orignac, “Glistenings on intraocular lenses in healthy eyes: effects and associations,” J. Refract. Surg. 27(12), 869–875 (2011).
25. G. Christiansen, F. J. Durcan, R. J. Olson, and K. Christiansen, “Glistenings in the AcrySof intraocular lens: pilot study,” J. Cataract Refract. Surg. 27(5), 728–733 (2001).
26. M. van der Mooren, L. Franssen, and P. Piers, “Effects of glistenings in intraocular lenses,” Biomed. Opt. Express 4(8), 1294–1304 (2013).
27. D. M. Saylor, D. Coleman Richardson, B. J. Dair, and S. K. Pollack, “Osmotic cavitation of elastomeric intraocular lenses,” Acta Biomater. 6(3), 1090–1098 (2010).
28. R. F. Fedors, “A new mechanism of failure in polymers,” J. Polym. Sci. Polym. Lett. Ed. 12(2), 81–84 (1974).
29. R. F. Fedors, “Osmotic effects in water absorption by polymers,” Polymer (Guildf.) 21(2), 207–212 (1980).
30. R. F. Fedors, “Cracking in a glassy epoxy resin induced by water absorption,” Polymer (Guildf.) 21(6), 713–715 (1980).
31. A. Thomas and K. Muniandy, “Adsorption and desorption of water in rubbers,” Polymer (Guildf.) 28(3), 408–415 (1987).
32. L. Gautier, B. Mortaigne, V. Bellenger, and J. Verdu, “Osmotic cracking in unsaturated polyester matrices under humid environments,” J. Appl. Polym. Sci. 79(14), 2517–2526 (2001).
33. A. Miyata, N. Uchida, K. Nakajima, and S. Yaguchi, “Clinical and experimental observation of glistenin in acrylic intraocular lenses,” Jpn. J. Ophthalmol. 45(6), 564–569 (2001).
34. B. E. Thomas and T. A. Callaghan, “Evaluation of in vitro glistening formation in hydrophobic acrylic intraocular lenses,” Clin. Ophthalmol. 7, 1529–1534 (2013).
35. N. Z. Grigorov, T. S. Spencer, N. Mamalis, and R. J. Olson, “In vitro comparison of glistening formation among hydrophobic acrylic intraocular lenses(1),” J. Cataract Refract. Surg. 28(7), 1262–1268 (2002).
36. T. Shiba, K. Mitooka, and H. Tsuneoka, “In vitro analysis of AcrySof intraocular lens glistening,” Eur. J. Ophthalmol. 13(9-10), 759–763 (2003).
37. K. Kato, M. Nishida, H. Yamane, K. Nakamae, Y. Tagami, and K. Tetsumoto, “Glistening formation in an AcrySof lens initiated by spinodal decomposition of the polymer network by temperature change,” J. Cataract Refract. Surg. 27(9), 1493–1498 (2001).
38. E. Smith and G. Dent, Modern Raman Spectroscopy - A Practical Approach (John Wiley & Sons Ltd, 2005).
39. D. W. Shipp, F. Sinjab, and I. Notingher, “Raman spectroscopy: techniques and applications in the life sciences,” Adv. Opt. Photonics 9(2), 315–428 (2017).
40. F. Siebert and P. Hildebrandt, Vibrational Spectroscopy in Life Science (Wiley, 2008).
41. M. S. Amer, Raman Spectroscopy for Soft Matter Applications (John Wiley & Sons, 2009).
42. H. G. M. Edwards, A. F. Johnson, and I. R. Lewis, “Applications of Raman spectroscopy to the study of polymers and polymerization processes,” J. Raman Spectrosc. 24(8), 475–483 (1993).
43. J. Popp and T. Mayerhöfer, Micro-raman Spectroscopy: Theory and Application (De Gruyter, 2018).
44. G. Rusciano, P. Capriglione, G. Pesce, S. Del Prete, G. Cennamo, D. Di Cave, L. Cerulli, and A. Sasso, “Raman microspectroscopy analysis in the treatment of acanthamoeba keratitis,” PLoS One 8(8), e72172–e72135 (2013).
45. G. Rusciano, G. Zito, G. Pesce, S. Del Prete, G. Cennamo, A. Sasso, “Assessment of conjunctival microvilli abnormality by micro-Raman analysis” J. Biophotonics (5), 551–559 (2016).
46. A. Bertoluzza, P. Monti, J. V. García-Ramos, R. Simoni, R. Caramazza, and A. Calzavara, “Applications of Raman spectroscopy to the ophthalmological field: Raman spectra of soft contact lenses made of poly-2-hydroxyethylmethacrylate (PHEMA).” J. Mol. Struct. 143, 469–472 (1986).
47. A. Bertoluzza, P. Monti, R. Simoni, R. Caramazza, M. Cellini, L. De Martino, and A. Calzavara, “Applications of Raman spectroscopy to ophthalmological field: Raman spectra of soft contact lenses made of polyvinylpyrrolidone,” in Laser Scattering Spectroscopy of Biological Objects (Studies in Physical & Theoretical Chemistry), J. Stepanek, P. Anzenbacher, and B. Sedlacek, ed. (Elsevier, 1987), vol 45, pp. 595–604.
48. A. Bertoluzza, C. Fagnano, P. Monti, G. Semerano, J. V. Garcia-Ramos, R. Caramazza, and M. Cellini, “Raman spectra of intraocular lenses before and after implantation in relation to their biocompatibility,” J. Raman Spectrosc. 18(2), 151–152 (1987).

49. P. Monti and R. Simoni, “The role of water in the molecular structure and properties of soft contact lenses and surface interactions,” J. Mol. Struct. 269(3–4), 243–255 (1992).

50. P. Monti, R. Simoni, R. Caramazza, and A. Bertoluzza, “Applications of Raman spectroscopy to ophthalmology: spectroscopic characterization of disposable soft contact lenses,” Biospectroscopy 4(6), 413–419 (1998).

51. K. Krysztofiak, K. Ciężar, and M. Kościński, “Raman imaging of layered soft contact lenses,” J. Appl. Biomater. Funct. Mater. 15(2), e149–e152 (2017).

52. United States Patent: US6636299B1, (2003).

53. G. Rusciano, A. Martinez, G. Pesce, G. Zito, and A. Sasso, “Micro-Raman analysis of glisterings in intraocular lenses,” Proc. SPIE 10333 Optical Methods for Inspection, Characterization, and Imaging of Biomaterials III, 103331A (2017).

54. H. Zhu, K. C. Jha, R. S. Bhatta, M. Tsige, and A. Dhinojwala, “Molecular structure of poly(methyl methacrylate) surface. I. Combination of interface-sensitive infrared-visible sum frequency generation, molecular dynamics simulations, and ab initio calculations,” Langmuir 30(39), 11609–11618 (2014).

55. B. Schneider, J. A. Štokr, P. Schmidt, M. Mihailov, S. Dirlikov, and N. Peeva, “Stretching and deformation vibrations of CH2, C(CH3) and O(CH3) groups of poly(methyl methacrylate),” Polymer (Guildf.) 20(6), 705–712 (1979).

56. S. Dirlikov and J. Koenig, “Assignment of the carbon-hydrogen stretching and bending vibrations of poly(methyl methacrylate) by selective deuteration,” Appl. Spectrosc. 33(6), 555–561 (1979).

57. H. Willis, V. Zichy, and P. Hendra, “The laser-Raman and infra-red spectra of poly(methyl methacrylate),” Polymer (Guildf.) 10(9), 737–746 (1969).

58. J. Lipschitz, “The vibrational spectrum of poly(methylmethacrylate): A review,” Polym. Plast. Technol. Eng. 19(1), 53–106 (1982).

59. K. J. Thomas, M. Sheeba, V. P. N. Nampoori, C. P. G. Vallabhan, and P. Radhakrishnan, “Raman spectra of polymethyl methacrylate optical fibres excited by a 532 nm diode pumped solid state laser,” J. Opt. A, Pure Appl. Opt. 10(5), 055303 (2008).

60. S. C. Goheen, R. M. Saunders, S. D. Harvey, and P. C. Olsen, “Raman spectroscopy of 2-hydroxyethyl methacrylate-acrylamide copolymer using gamma irradiation for cross-linking,” J. Raman Spectrosc. 37(11), 1248–1256 (2006).

61. F. Pallikari, G. Chondrokoukis, M. Rebekakis, and Y. Kotsalas, “Raman spectroscopy: A technique for estimating extent of polymerization in PMMA,” Mater. Res. Innov. 4(2–3), 89–92 (2001).

62. X. Xu, H. Ming, Q. Zhang, and Y. Zhang, “Properties of Raman spectra and laser induced birefringence in polymethyl methacrylate optical fibres,” J. Opt. A, Pure Appl. Opt. 4(3), 237–242 (2002).

63. C. Choe, J. Lademann, and M. E. Darvin, “Depth profiles of hydrogen bound water molecule types and their relation to lipid and protein interaction in the human stratum corneum in vivo,” Analyst (Lond.) 141(22), 6329–6337 (2016).