Materials for intraocular lenses (IOLs): Review of developments to achieve biocompatibility

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Abstract: It is true that the developments in material sciences along with the improvements in various aspects of technology involved in transforming materials into products, over the years, have been responsible for making many of the impossible-looking devices possible. It is also a fact that the demand for a new, improved and better material has never ended; in fact it has been increasing to a greater degree and with bigger dimensions than ever before, especially in recent times. As a matter of fact, for certain advanced applications, the need for efforts to have new materials can never be over emphasized; for example, in the area of biomedical devices such as intraocular lens (IOL). The advances in the field of bio-medical applications require the materials of high quality meeting stringent norms of performance. For implants such as the ones like IOL used for correction of vision of the eyes, besides the quality and performance of materials, biocompatibility is an issue of major concern. The material scientists have been working on the development of materials for IOLs targeting the needs arising out of the developing countries. The challenges include not only to bring down the cost of the materials used for IOLs but also to increase the biocompatibility of IOLs. For making the development process easy and bringing the state-of-the-art of knowledge to those looking for new materials, it is thought necessary to review various facets of IOLs in the present paper. Not only the aspects related to the recent developments in biomedical devices of eye care but also related to the properties of available materials vis-a-vis the deficiencies in properties of existing materials have been covered in this review. The aim has been to bring out the gap areas at various levels of process of product chain starting from the monomer to polymer, blank to IOL, insertion of IOL into eyes to life cycle of IOLs, mainly to provide certain possible and feasible leads to meet the challenges of making new and more biocompatible materials.

Keywords: Intraocular lens; Cataract; Biocompatibility; Heparin; Hyaluronic acid

Introduction

IOLs have become the established device for treatment of patients suffering from the common eye disease called cataract.

Cataract develops majorly due to long term exposure to radiations such as ultra violet and secondary effects of diseases such as diabetes and malnutrition. They are usually a result of denaturation of lens proteins. Genetic factors are often a cause of congenital cataract and positive family history may also play a role in predisposing someone to cataract at an early age; a phenomenon of “anticipation” in pre-senile cataracts. Cataract may also be produced by eye injury or physical trauma. One third of pediatric cataracts are sporadic; they are not associated with any systemic or ocular diseases. However, there may be spontaneous mutations and may lead to cataract formation in the patient’s offsprings. As many as 23% of congenital cataracts are familial. This type
of cataract may appear as a total cataract, polar cataract, lamellar cataract, or nuclear opacity. All close family members should be examined.

A study among Iceland air pilots showed commercial airline pilots as three times more likely to develop cataract as people with non-flying jobs. This is thought to be caused by excessive exposure to radiations coming from outer space [1]. Cataracts are usually also common in persons exposed to infrared radiations and glassblowers who suffer from “exfoliation syndrome” is an example of exposure to radiations. Exposure to microwave radiations can also cause cataracts. At times, use of certain drugs can induce development of cataract, such as corticosteroids [2].

Preventive measures have also been taken to prevent the formation of cataract [3]. Further, in the event of the cataract becoming incurable, several techniques have been developed to correct the vision. Certain modern methods which have been in use for quite some time are so patient-friendly that the correction is achieved even without surgery. One such technique involves the use of intra-ocular lens where a very thin optical plastic lens of the power as per the desired correction of the power of the eye is inserted. Various types of materials have been developed for making of the IOLs. With the advancement of science, the need for newer materials for IOLs has always been there. Moreover, the fact that the IOLs remain inside the eye, the biocompatibility of IOLs is the cause of concern for the material scientist’s world over. The present paper elaborates various aspects related to the development of materials with improved biocompatibility for making IOLs.

**Intraocular lenses**

*Treatment of cataract*

Cataracts are treated surgically by removing the lens. The cataract surgery results in a condition called “aphakia”, “without a lens” and it is necessary to provide an artificial lens for the eye to have vision. Currently in India, and until the 1970s in United States, this lens has been provided in the form of very thick glasses, known as aphakic glasses.

The most frequently employed surgical techniques for treatment of cataract are extra capsular extraction and phacoemulsification. Surgery involves the replacement of the natural lens of the eye with the intraocular lens [4].

Like all the other requirements of materials for a given application, the development of a suitable material for IOL’s has always been a challenge. Based on the needs depending upon the extent and type of correction of vision, procedure of correction of vision, conditions of the patient etc. the demand for materials with complete biocompatibility besides the essential physico-mechanical as well as the optical properties has been rising. In order to design materials for such critical biomedical devices, various aspects of material sciences along with the requirement related to the application of materials will have to be understood, while taking into account the deficiencies with the existing materials.

*Uses of IOLs*

The first Intraocular lenses used were made of glass, which were heavy and prone to shatter during Nd:YAG capsulactomy. Even though plastic materials were in use for several industrial applications, their use as intraocular lenses started only when someone noticed that pieces of shattered windshields made up of PMMA in the eyes
of the pilots of World War II did not show any rejection or foreign body reaction. Polymethylmethacrylate was thus the first plastic material to be used successfully in intraocular lenses. Advances in technology have brought about the use of silicon and acrylic, both of which are soft and foldable inert materials. This allows the lens to be folded and inserted into the eye through a smaller incision. PMMA and acrylic lenses can also be used with smaller incisions and are a better choice in people who have a history of uveitis, have diabetic retinopathy requiring vitrectomy with replacement by silicon oil or are at high risk of retinal detachment.

Intraocular lenses are not only used for cataract treatment but are being used also in several types of refractive eye surgery. They are used in the treatment of presbyopia, phakic treatment of myopia [5] and for phakic treatment for hyperopia [6]. Several new refractive eye surgery procedures now rely on intraocular lenses rather than laser surgery to correct vision deficiencies.

Also under FDA investigation is an intraocular lens that holds promise for correcting presbyopia, the vision problems that occurs when the natural lens of the eye become less flexible.

Materials for IOL

From the above discussion, it is quite obvious that the IOLs are designed to remain inserted in the eye as an integral part of eye playing the role of a naturally existing crystalline lens of the eye. Thus, it is essential that the material to be used for making IOLs must meet the following basic criteria related to:

(a) Body reaction: It should be compatible with the body without any adverse body reaction; biocompatible.

(b) Life cycle: It must not degrade, decompose, react or disappear during the entire period of its usage i.e. at least for the expected life of a human; stable and inert.

(c) Performance: It must exhibit the optical characteristics to serve as the vision-provider to the user just like the naturally occurring lens of the eye. For this, it is essential that all necessary optical properties such as density, refractive index, optical transmittance, dimensional stability, mechanical properties, biocompatibility, toxicity and chemical stability must be ensured before reducing the material for IOL; excellent optical properties.

(d) Insertion: It must be of a chemistry which ensures that the material is inserted into the eye without any problems and with the available techniques of eye correction through-surgery etc; very thin and flexible.

Currently, IOLs composed of four basic materials are available for replacement lenses of silicone, acrylic (hydrophilic and hydrophobic) and polymethyl methacrylate [7]. Each material though proven safe for implantation provides its own specific advantages and disadvantages.

In the selection of a material for intraocular lenses especially foldable intraocular lenses, criteria that are important are glass transition temperature, elongation and tack of the material [8]. The properties of the monomers should be such that the polymer should have a glass transition temperature not greater than 37 °C, which is the normal body temperature. Polymers having a glass transition temperature higher than 37°C are not suitable, since such lenses could be rolled or folded only at temperature above 37 °C and would not unroll or unfold at normal body temperature. It is preferred to use
polymers having a glass transition temperatures below normal body temperature and no greater than normal room temperature, so that the lenses can be folded or rolled conveniently at room temperature.

Another important property of intraocular lenses is their mechanical strength. The lenses must exhibit sufficient strength to allow them to be folded without fracturing. Polymers exhibiting an elongation of 150-200% are preferred. Lenses made from polymers having an elongation of less than 150% are able to reduce the distortion, which occurs when they are rolled or folded. Elongation (%) is an important property where the IOL material should preferably have an elongation of 150 %-200 %. This indicates that an IOL optic made of the material generally will not crack, tear or split when folded [9-10].

The tackiness of an IOL is expressed in terms of Tack Quotient; where the ratio of the tack of the test material to that of the standard material is referred to as Tack Quotient. IOL materials having a Tack Quotient 1-1.5 are preferred.

PMMA has been the standard IOL material since the surgical approach was first developed by Harold Ridley in 1949. The IOL is generally lathe cut from PMMA rods or buttons. The standard IOL consists of a central optic, which is supported by haptics, projections from the main body of the lens, which provide support in the eye. The haptics are usually constructed from PMMA or the base material of the optic although other polymers may be used. Current lenses usually employ a 7mm diameter optic, a 6.5 mm oval-shaped optic or a 5 mm round optic.

Attempts to improve the biocompatibility of IOLs have included: process modification to produce a highly polished surface; the generation of both soft, high-energy surfaces using NVP and HEMA and hard low energy surfaces using perfluoropropane; and the binding of heparin and hyaluronic acid to the outer surface of the lens. More recently the use of phosphorylcholin-based polymeric coatings has been reported [11]. These latter coatings were shown to reduce protein adsorption, cellular adhesion and neutrophil activation by the PMMA surface [12] and were shown in vivo to reduce cellular deposition onto the lens [13].

Phacoemulsification, with its small incision, has encouraged the development of foldable IOL for implantation. The need to insert these devices through a 3.5mm incision has also encouraged companies to investigate other design modalities including the concept of plate design IOLs. These foldable lenses have been manufactured from silicon elastomers, collagen copolymers, PHEMA hydrogels and ‘acrylic’ polymers (Table 1). In developing these materials, particular emphasis has been placed on the handling, foldability and unfolding characteristics of the lenses since they must be easy to insert. It has been reported that the acrylic lens unfolds more slowly and in a more controlled fashion than the silicon lenses; the higher refractive index of the acrylic material gives rise to a thinner IOL. Evidences suggest that the hydrophilic materials are less damaging to the corneal endothelium and produce lower level of inflammatory response in terms of cellular adhesion and foreign body response when compared to PMMA IOLs. Recent studies have also suggested that phosphorylcholin-based acrylate polymers may have application in the development of novel biocompatible foldable IOLs.

Recent emphasis has focused on the development of materials, which will reduce Posterior Capsule Opacification (PCO). This phenomenon is attributed to the migration of lens epithelial cells across the posterior capsule bag. Although this ‘secondary cataract’ can be treated using a YAG laser to rupture the capsular bag, poor focusing
can result in dislocation, decentralization, fragmentation and pitting of PMMA lenses. Acrylic, silicone and HEMA IOL’s have been shown to be more tolerant to the YAG laser than PMMA. Furthermore, recent in vivo studies have suggested that PCO occur less often following implantation of acrylic IOL than other materials. This may be attributed to the physical inhibition of lens cell migration by adhesion of the posterior capsule to the IOL following implantation. Other approaches that have been investigated to reduce PCO include the modification of the IOL surface with anti-metabolites. Although these approaches appear to be effective in in-vitro models there are some concerns over the effects of these anti-metabolites on other ocular tissues.

Tab. 1. Examples of Intraocular lens materials (modified from Kohen [15]).

<table>
<thead>
<tr>
<th>Lens type</th>
<th>Material</th>
<th>Refractive Index</th>
<th>Water Content</th>
<th>Property</th>
</tr>
</thead>
<tbody>
<tr>
<td>PMMA</td>
<td>MMA</td>
<td>1.49</td>
<td>&lt;1%</td>
<td>Rigid</td>
</tr>
<tr>
<td>PMMA with HSM</td>
<td>MMA</td>
<td>1.49</td>
<td>&lt;1%</td>
<td>Rigid</td>
</tr>
<tr>
<td>Alcon Acrylsof</td>
<td>PEA/PEMA</td>
<td>1.55</td>
<td>&lt;1%</td>
<td>Foldable</td>
</tr>
<tr>
<td>Allergan Clariflex</td>
<td>EA/EMA/TFEMA</td>
<td>1.47</td>
<td>&lt;1%</td>
<td>Foldable</td>
</tr>
<tr>
<td>ORC MemoryLens</td>
<td>HEMA/MMA</td>
<td>1.47</td>
<td>20%</td>
<td>Foldable</td>
</tr>
<tr>
<td>Storz Hydroview</td>
<td>HEXMA/HEMA</td>
<td>1.47</td>
<td>18%</td>
<td>Foldable</td>
</tr>
<tr>
<td>Alcon HydroSof</td>
<td>HEMA</td>
<td>1.44</td>
<td>38%</td>
<td>Foldable</td>
</tr>
<tr>
<td>Chiron C10UB</td>
<td>PDMS</td>
<td>1.41</td>
<td>&lt;1%</td>
<td>Foldable</td>
</tr>
<tr>
<td>Adatomed 90D</td>
<td>PDMS</td>
<td>1.41</td>
<td>&lt;1%</td>
<td>Foldable</td>
</tr>
<tr>
<td>Staar AA-4203</td>
<td>PDMS</td>
<td>1.41</td>
<td>1%</td>
<td>Foldable</td>
</tr>
<tr>
<td>Allergan SI-30NB/SI-40NB</td>
<td>PDMS</td>
<td>1.41</td>
<td>&lt;1%</td>
<td>Foldable</td>
</tr>
<tr>
<td>ioIab Soflex</td>
<td>PDMDPS</td>
<td>1.43/1.46</td>
<td>&lt;1%</td>
<td>Foldable</td>
</tr>
<tr>
<td>Domilens Silens</td>
<td>PDMDPS</td>
<td>1.43/1.46</td>
<td>&lt;1%</td>
<td>Foldable</td>
</tr>
<tr>
<td>Pharmacia Cee ON 920</td>
<td>PDMDPS</td>
<td>1.43/1.46</td>
<td>&lt;1%</td>
<td>Foldable</td>
</tr>
<tr>
<td>AllerganSI-18NGB/SI-26NB</td>
<td>PDMDPS</td>
<td>1.43/1.46</td>
<td>&lt;1%</td>
<td>Foldable</td>
</tr>
</tbody>
</table>

PMMA: poly(methyl methacrylate); MMA: methyl methacrylate; PEA: 2-phenethyl acrylate; PEMA: 2-phenethyl methacrylate; EA: ethylacrylate; EMA: ethyl methacrylate; TFEMA: 2,2,2-trifluoroethyl methacrylate; HEXMA: 6-hydroxyethyl methacrylate; PDMS: poly(dimethylsiloxane); PDMDPS: poly(dimethyldiphenylsiloxane).

Unlike the natural crystalline lens, standard IOL provide no means of accommodation for near and far vision. In most cases the visual adjustment is achieved through the wearing of standard spectacles. Various approaches have been described for the fabrication of lenses that utilizes the natural muscular action exerted on the capsular bag as a mean of accommodation. A two-piece lens system has been patented in which the distance between the two lenses is controlled by the pressure exerted by the ciliary muscles on a U-shaped flange connecting the periphery of the two lenses. Relaxation of the ciliary muscle causes the lens to flatten thereby changing the focal distance of the lens [15].

Other approaches include the use of viscoelastic IOL implants, which may be injected into the capsular bag following removal of the natural crystalline lens. The viscoelastic gel’s dimensions and refractive properties are modified as the ciliary muscle contracts and relax changing the capsular bag to either stretch or bulge, respectively [16].
Recent concerns over the potential damage to the posterior segment of the eye arising from UV radiation following removal of the natural crystalline lens has encouraged companies to include UV absorbing chromophores in IOL materials. These chromophores are generally derivatives of benzotriazole, which absorb UV radiation below 400 nm and are either physically blended or chemically incorporated into the IOL material.

Types of IOL

Depending upon the surgical procedure, IOLs can be of two types

1. Phakic IOL [14] [15]
2. Aphakic IOL [15]

Phakic IOL: Phakic intraocular lenses, or phakic lenses, are made of plastic materials or silicones that are implanted into the eye permanently to reduce a patient's need for glasses or contact lenses. Phakic refers to the fact that the lens is implanted into the eye without removing the eye's natural lens. During phakic lens implantation surgery small incision is made in front of the eye. The phakic lens is inserted through the incision and placed just in front of or just behind the iris.

Tab. 2. Different types of aphakic IOLs available in the market are mentioned below [16].

<table>
<thead>
<tr>
<th>Phakic IOL</th>
<th>Aphakic IOL</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Anterior chamber, rigid lenses</td>
<td></td>
</tr>
<tr>
<td>- Posterior chamber pseudo-phakic, piggy back, multifocal</td>
<td></td>
</tr>
<tr>
<td>- Posterior chamber, rigid lenses</td>
<td></td>
</tr>
<tr>
<td>- Posterior chamber, foldable, no edge modification, haptic plates lenses</td>
<td></td>
</tr>
<tr>
<td>- Posterior chamber, foldable, no edge modification lenses</td>
<td></td>
</tr>
<tr>
<td>- Posterior chamber, foldable, posterior edge modification lenses</td>
<td></td>
</tr>
<tr>
<td>- Posterior chamber, foldable, anterior and posterior edge modification lenses</td>
<td></td>
</tr>
<tr>
<td>- Posterior chamber, foldable, multifocal/bifocal lenses</td>
<td></td>
</tr>
<tr>
<td>- Posterior chamber, foldable, anterior and posterior edge modification, multifocal/bifocal lenses</td>
<td></td>
</tr>
<tr>
<td>- Posterior chamber, foldable, multifocal, accommodative lenses</td>
<td></td>
</tr>
<tr>
<td>- Anterior chamber, rigid lenses, anterior chamber</td>
<td></td>
</tr>
</tbody>
</table>

Phakic lenses are used to correct refractive error, in other words, the error in the eye's focusing power. Currently all phakic lenses approved by the FDA e.g. anterior chamber, rigid lenses are for the correction of near sightedness (myopia). Ideally, phakic lenses cause light entering the eye to be focused on the retina providing clear distance vision without the aid of spectacle lenses or contact lenses [14].
Aphakic IOL: Aphakic intraocular lenses are implanted in the eye after removing the cloudy natural lens (cataract) of the eye, by surgery [14]. Cataract surgery results in a condition called “aphakia” which means “without a lens”. Thus the lenses implanted to correct this situation are called aphakic IOLs (Table 2) [15] [17].

Manufacturing of IOL

-Polymerization techniques to make materials for IOLs

The process for the production of IOLs consists of the following steps:

(a) Co-polymerization of monomers
(b) Casting into blanks / lenses
(c) Machining, cutting and grinding
(d) Fixing of the haptic to the optic.

(a) Co-polymerization: The polymers for foldable intraocular lenses and rigid intraocular lenses are made by the conventional polymerization method. A mixture of the liquid monomers in the desired proportion, together with a conventional thermal free -radical initiator and is injected into a suitable mold consisting of the optic and haptic portions.

(b) Cast polymerization: The mixture is then subjected to a heating cycle to activate the initiator. Free radical initiator such as peroxides (benzophenone peroxide), peroxycarbonates such as bis-(4-t-butyldicyclohexyl) peroxydicarbonates and azonitriles such as azobisisobutyronitrile are used. To facilitate the polymerization, conventional photo initiator compounds are also used.

Optional additives such as UV absorbing materials are used so that the lenses may have an ultraviolet absorbance approximately that of the natural lens of the eye. The ultraviolet absorbing material can be any compound that absorbs ultraviolet light but does not absorb substantial amounts of visible light. The ultraviolet absorbing compound is incorporated into the monomer mixture and entrapped in the polymer matrix when the monomer mixture is polymerized [18]. To present leaching out of the ultraviolet absorbing compound, compounds that can covalently bond to the polymer matrix are chosen. Examples of such compounds are substituted hydroxy benzophenones. The other forms of polymerization include bulk, suspension, emulsion or solution polymerization.

IOLs can also be cast into sheet form by a conventional 2-step procedure [21]. In the first step, the casting mixture is prepared by heating the mixture of monomers, cross-linking agent and initiator at a temperature of 80 °C. The second step is the transfer of the mix to a cell suitable for casting sheets and polymerized by subjecting the cell to suitable heating. IOLs are the lathe cut from of the sheets while holding the temperature of the sheets below 0 °C [22].

(c) Cutting, grinding and machining: After the polymerization cycle, molding and drilling operations are carried out. The mold containing the optical material is placed on a lathe and the desired optic chamber is lathe cut. The lathing and drilling operation is carried out by cooling the mold/optic in a freezer to less than 10 °C and preferably less than 0 °C [19].
(d) Attachment of the haptics: The next step involves the attachment of the haptic to the optic in the case of a multipiece IOL. Two halves are drilled into the side of the lens. The haptic is then inserted into the optic with the help of a laser source [20]. Suitable haptic materials are polypropylene and polymethylmethacrylate.

Techniques of making IOLs from base materials

Rigid intraocular lens made of PMMA (Polymethyl methacrylate) and soft intraocular lens made of modified acrylates or silicones can be manufactured by the method

1. Cast molding: - A method of injecting a monomer into a casting mold designed to produce lenses of a desired shape. Cast molding is also used to cast optical blanks, which are further processed into lenses.

2. Lathe cutting: - A method of cutting a sheet obtained by polymerizing and curing of a monomer into an intraocular lens of a desired shape. Another alternative is to use the optical blanks and subjecting it to the lathe machine from which lenses can be cut out.

It has been reported that in the IOLs manufactured by the methods as mentioned above, problem of voids formation in the base material for the IOL during polymerization was observed. These voids in the base material get filled up with the vitreous humor of the eye and results in the formation of luminescent spots which does not affect the visual activity, it affects the contrast sensitivity of the IOL [23]. Ichikawa, et al developed a multi step process to overcome the problem of void formation as detailed below:

Step 1: The monomer mixed solution is polymerized to produce a base material.

Step 2: One part of the base material produced in the first step is heated in oven to completely terminate the polymerization.

Step 3: The completely polymerized material from above step immersed into the second portion of the base material produced during the step1. This is basically to impregnate the material on to, so that in case any voids formed in the polymerized material can be filled by the base material.

Step 4: The impregnated material from above step is taken out and excess of the unpolymerized base material is removed from the surface.

Step 5: The setting of a protective coating is done after removing the excess of the unpolymerized material from the surface of the base material as in step 4.

Step 6: Finally the polymerization of the material of step 5 is done [23].

Basically, this method was earlier tried for preparation of other polymeric materials such as Polyvinyl chloride to eliminate the voids also termed as fish eye. The multi-step process of making IOLs is useful in that respect. By adopting suitable methodology for preparation of IOLs, certain biocompatibility problems could be resolved. For example, according to one invention, a bicomposite IOL optic comprising an anterior surface material consisting of an ophthalmically acceptable lens-forming material and a posterior surface material, different from the anterior surface material, for reducing the risk of posterior capsule opacification is prepared. The posterior surface material consisted essentially of two or more aryl acrylic hydrophobic functional monomers. The method of preparation of IOLs involves the following steps:

(a) Forming a posterior surface layer of material by polymerizing a posterior surface material composition consisting essentially of two or more aryl acrylic hydrophobic
monomer and a cross linking agent in a mold having the desired IOL posterior surface shape and by

(b) Forming an anterior surface layer by adding a liquid anterior composition consisting of an ophthalmically acceptable IOL material to the top of the posterior surface layer and polymerizing the liquid anterior composition.

Yet another method for producing IOLs include a combination of steps which helped to increase the pull strength between the fixation member of the IOL and the optic of the IOL without requiring sophisticated high frequency corona discharge activation or plasma activation of the fixation member or primer coating of the fixation member.

While it may appear simple, achieving the complete polymerization to obtain a material of desired characteristics without any flaws as far as the optical properties is considered always remains a subject of research and development, in spite of the existing experience of so many years and for several types of materials.

Attempts to resolve the biocompatibility-related issues by developing novel methods of preparation of IOLs are a welcome trend. As far as the concept of providing a single material with completely different surfaces is concerned, it presents several opportunities if one looks at the challenges.

Problems with IOL

In spite of the fact that the experience of using PMMA for IOL for more than 50 years has been satisfactory to demonstrate that these lenses are relatively inert but they cannot be called as perfectly biocompatible. It is well documented in the literature that a significant disadvantage inherent to PMMA IOLs resides in the fact that even brief, non-traumatic contact between corneal endothelium and PMMA surface results in extensive damage to the endothelium [24]. Posterior capsule opacification is another major problem noticed commonly with available IOL that occurs because of the localized release of different cytokins, including transforming growth factor beta and fibroblast growth factors [25]. The implantation of intraocular lenses (IOLs) following cataract surgery also induces a foreign body reaction of the IOL and a lens epithelial cell reaction [17]. It was evaluated by extensive clinical investigations of the different intraocular lenses that biomaterial properties are a key factor that influences the quantity of monocytes/macrophages and the process of their maturation/senescence. Lens epithelial cell (LEC) outgrowth is influenced both by the biomaterial of IOLs and by the monocyte/macrophages reaction [26].

Materials having the lowest contact angle are found to be more biocompatible [27], although heparin modified surface show lowest contact angle but still some fibrous reaction and posterior capsule opacification was observed with these lenses [28]. In heparin surface modified IOLs, heparin surface defects after YAG laser treatment was observed due to which decreased heparin effect in vivo could be possible [29]. After selecting the best biomaterials and after modifying the surface of the IOL, biocompatibility is improved but still lower grade of inflammatory cell adhesion, anterior capsule opacification (ACO) [27] and other problems associated with IOLs was found. Various agents have been used in conjunction with scleral buckles in the treatment of retinal detachment. These agents are injected into the eye to provide an intravitreal tamponade. Silicone oil is the most commonly used material, for this purpose but silicon oil emulsification and adherence in the eye results in poor biocompatibility [30] [31]. By making the lens surface hydrophilic using certain polysaccharides, the reduced potential silicon oil can be significantly reduced [31].
**Biocompatibility of IOL**

**Biocompatibility**

A “biocompatible” material is one that does not cause significant adverse reactions (e.g., toxic or antigenic responses) in the body, whether it degrades within the body, remains for extended periods of time, or is excreted whole. [32].

**Criteria of biocompatibility**

Ideally a biocompatible material will:

1. Not induce undesirable reactions in the human body; blood clotting, tissue death, tumor formation, allergic reaction, foreign body reaction (rejection), inflammation etc.
2. Have the desired physical properties; mechanical strength, elasticity, permeability flexibility etc.
3. Substantially maintain its properties and function during the time that it remains implanted in or in contact with the body; whether for hours or for lifetime. In other words it will be completely inert with specified behavior of degradation. [33]
4. Be easy to purify, fabricate, sterilize etc.

**Processes to improve biocompatibility**

The various approaches tried to achieve biocompatibility are:

(a) **Chemical composition:**

A study by Dr. Samuelson and his colleagues found that the type of the material of construction of the IOL was the most important predictive factor for the formation of inflammatory deposits [34]. From this we get the approach of achieving biocompatibility by changing the chemical composition or by incorporating suitable biocompatible monomers during the manufacturing process. Using this approach antimicrobial materials were tried. Another similar approach for improving durability and optical accuracy involves the copolymerization of poly(methylmethacrylate) or methylmethacrylate and ethylene glycol dimethacrylate by the thermo pressure extension method [35].

It was observed that hydrophilicity of the IOLs prevents the attachment of the cells and the softness of the IOLs reduced the damage against Nd: YAG laser photodisruption. Both of these two properties of the IOLs are responsible for the decreased simulation of granulocytes and reduced corneal endothelial damage [40], thus the improvement of hydrophilicity and softness of IOL is also one of the ways to improve biocompatibility. From this point of view, hydrophilic 2-phenylethylacrylate and 2-phenylethyl methacrylate copolymer-based materials are useful in the manufacture of intraocular lenses with minimized risk for glistening. Comparison of various lenses evaluate that the lenses made of these monomers show significantly less posterior capsule opacification than those with silicon or heparin surface modified IOL with a round-edged design [28]. A further small increase in the hydrophilicity of these materials can prevent the opacification of the lenses.

Incorporation of certain biochemicals which are already present in the biological system can be tried e.g. polyurethanes, polyolefines, vinyl polymers, acrylic polymers, polyamides, polyesters, polysiloxanes etc. can be rendered biocompatible by including
with the polymeric material, hyaluronic acid as a salt [41], which in general is characterized by notable viscosity, slipperiness, and ability to reduce friction. This is the basis of its presence in bodies of humans and animals [36].

In another approach to improve biocompatibility, reactive and hydrophilic polymers are used to form covalent chemical linkages with the surface of IOLs. The preferred reactive, hydrophilic polymers have complementary chemical functionalities to that of the functional groups contained in the polymeric material of the IOL. Such a complementary chemical functionality enables a chemical reaction between the functional groups of the polymeric material of the IOL and the reactive, hydrophilic polymer to form covalent chemical linkages. Such surface modification of an IOL implant reduces or eliminates silicon oil adsorption upon subsequent exposure, reduces or eliminates surface calcification, reduces or eliminates lens epithelial cell surface growth and/or reduces friction upon passage through an inserter for implantation [37].

A biocompatibilizing process is also known which involves radical polymerization using ethylenically unsaturated monomers; a polymer having pendant zwitterionic groups bearing a center of permanent positive charge and other pendant groups that are capable of binding the polymer to a surface is used. Such coatings bind to the surface with good adhesion and are not removable in the environment in which the coated surfaces are used. Zwitterionic groups are known to mimic the structure of the head groups of phospholipids in cells, it is thought that the presence of such groups at a surface renders the surface biocompatible. [38] In another similar approach to improve biocompatibility radical polymerization of ethylenically unsaturated zwitterionic monomer containing a sulpho-betain zwitterionic group and a radical polymerizable ethylenically unsaturated comonomer containing a hydrophobic group is selected [39].

The co-polymerization of biocompatible monomers with monomers containing pendant amino groups has also shown promising results, Dimethyl amino ethyl methacrylate (DMAEMA) is one such monomer, which shows most cell adhesion. DMA group which is there in this monomer showed exceptional affinity for endothelial cells over platelets, which is a desirable property for blood contacting surfaces since one desires low thrombogenicity but a propensity for endothelialization [40].

(b) Chemical modification:

According to this approach fluorination was studied as one way to improve the biocompatibility, using this approach it was found that fluorinated PMMA are more stable than PMMA and the biocompatibility tests show that they are as biocompatible as PMMA. In the search for getting more biocompatible polymers, transparent polyamides were studied, which did not give superior results.

Surfaces can be chemically modified using plasma technology to introduce reactive groups onto the surface of polymer materials in a fast and effective manner [41]. Elan et al described a treatment with oxygen plasma followed by the application of 3-glycidoxypropyltrimethoxy silane and the surfaces thus treated are used for the formation of covalent bonds with polysaccharides [42, 43]. However, the total number of reactions, which involve functional groups immobilized on a surface and large molecules, such as polysaccharides, is seriously limited by the effect commonly known as steric hindrance. The large size of the polysaccharide molecule prevents or impedes contact between reactive groups so that the probability of an effective reaction taking place is reduced.
Under a similar approach, there are methods for modifying the surface of a material by forming activated sites by exposing the surface to Glow Discharge Plasma (GDP) such as Radio Frequency Glow Discharge Plasma (RF-GDP) or microwave GDP of sufficient power for a time required to activate and/or excite the surface of the material and optionally, subsequently exposing the surface to air or oxygen to form peroxy or hydroperoxy groups or other chemically reactive atomic or molecular species on the surface. This surface is exposed to a solution of an ethylenically unsaturated monomer or mixtures and polymerization is induced using gamma- or electron beam-irradiation. Covalent bonding to the active surface species by irradiating the surface with gamma or electron beam radiation is done [44]. Introduction of functional groups onto the surface of a polymeric material can be done by treatment with methanol plasma, followed by placing the material in contact with an epihydrochlorin solution which guarantees the presence of groups, suited to react with polysaccharides [45]. One way to introduce amino groups onto the surface of polymer substrates is by the use of ammonia plasma. The amino groups are then reacted with hyaluronic acid or other polysaccharides by the use of a condensing agent [42].

One more method for this purpose involves the treatment of polymeric materials with reactive solutions, so as to introduce negative electrostatic charges onto the surface itself. This treated surface is placed in contact with an aqueous solution of polyethylene imine (PEI) a polymer characterized by the presence of amino groups and a positive electrostatic charge. The interaction between the different charges binds PEI to the modified surface, to produce a surface rich in amino groups. Heparin and other polysaccharides can be bound to the aminated surface after treatment with nitrite solutions [46]. The reaction between PEI and any aldehyde groups present or introduced on the polysaccharide is however used to bind the polysaccharide in various conformations to the surface of the object [43]. Typically, the reaction between carboxyl groups of the polysaccharide and amino groups of the surface is promoted by ethylene dimethyl amino propyl carbodiimide (EDC) [47]. Moreover, unlike other polysaccharides, hyaluronic acid is only slightly sensitive to partial oxidation reactions, which allows reactive aldehyde-type groups to be introduced on the polysaccharide [37].

Keeping in view the benefits of heparin, lots of work has been done using the heparin. Towards the further advancement of this approach, there is one method for making improved heparinized biomaterial. In this approach heparinized surface is provided with an adsorbed protein, which may be activated by the immobilized heparin to block the coagulation of fibrinogen by thrombin. Several plasma proteins are known to inhibit the activity of thrombin and other serine proteases. Out of these AT-III is the preferred adsorbed protein since it may be activated by heparin to inhibit thrombin and also because it inhibits other serine protease of the coagulation pathway such as IX a, XI a, X a and XII. This can be achieved by the incubation of the heparinized surface in a HEPES buffer solution for a few minutes followed by rinsing the surface to remove non bonded antithrombin [48].

(c) Surface modification:

PMMA, which was the material used in the first IOL dating back to 1949 is still considered the gold standard by some cataract surgeons [49]. Since it is extremely difficult to avoid any contact between implant surfaces and endothelium during surgical procedures and especially to other sensitive ocular tissues during implant life, i.e., the iris, ciliary sulcus etc, efforts have been undertaken to modify the PMMA ocular implant surfaces to reduce the tendency to adhere to and damage corneal endothelium.
Ocular implant surfaces have been coated with various hydrophilic polymer solutions or temporary soluble coatings such as methylcellulose, polyvinylpyrrolidone, etc., to reduce the degree of adhesion between the implant surfaces and tissue cells [50]. While offering some temporary protection, these methods have not proven entirely satisfactory since such coatings complicate surgery, do not adhere adequately to the implant surfaces, become dislodged or deteriorate after implantation, dissolve away rapidly during or soon after surgery or may produce adverse post-operative complications. Moreover, it is difficult to control the thickness and uniformity of such coatings.

Yalon et al has reported attempts to produce protective coatings on PMMA implant surfaces by gamma irradiation induced polymerization of vinylpyrrolidone [51]. Their efforts were not altogether successful, however, since their methods also presented problems in controlling the optical and tissue protective qualities of the coatings. The resulting coatings were also of poor quality and nonuniform mechanical stability. Certain process conditions and parameters that produce thin hydrophilic gamma or electron beam irradiation induced polymerized and chemically grafted coatings of N-vinylpyrrolidone (NVP) polymer, co-polymerized NVP and 2-hydroxyethyl methacrylate (HEMA), or HEMA and their copolymers with ionic co-monomers on the surfaces of ocular implants constructed of materials including PMMA are known. These coatings increase the hydrophilicity of the implant surface and minimize adhesion between the surface and sensitive ocular tissues [52, 53]. They are thin, uniform, durable and less subject to removal, degradation or deterioration during or following surgery.

Goldberg et al have invented an advanced method for modifying the surface of a material adapted for contact with tissue to impart biofunctional properties to the surface [54]. The method comprises exposing the surface to a solution of an ethylenically unsaturated monomer and a biofunctional agent and irradiating the surface with gamma or electron beam to thereby form on the surface a graft polymerized coating having physically entrapped or chemically bonded molecules of the biofunctional agent which imparts biofunctional properties to the surface.

A method for making nonthrombogenic surfaces was disclosed where the surfaces were treated with a cationic surface-active agent as an intermediate layer and a conventional anticoagulant such as heparin as the top layer [55]. Some papers describe the use of an intermediate layer between the substrate and the hyaluronic acid coating [56, 57]. This intermediate layer physically adheres to the substrate and contains chemical groups which are suitable for the formation of a bond with the chemical groups of heparin/hyaluronic acid. As the intermediate layer is only physically attached to the substrate surface, which might not be very strong and stable, there is a risk of heparin or similar molecules becoming detached thereby reducing the effectiveness of the surface.

The surface of a polymeric object is treated with reactive solutions, so as to introduce negative charges onto the surface itself. The surface thus treated is placed in contact with an aqueous solution of polyethylene imine (PEI), a polymer characterized by the presence of amino groups and a positive charge. The interaction between the different charges binds PEI to the modified surface, to produce a surface rich in amino groups. Heparin and other polysaccharides are then bound to the aminated surface after treatment with nitrite solutions [58]. Although this process effectively solves the problem of introduction of reactive groups on the surface of the material, it is not so effective in binding the polysaccharides to the surface unless the activation of heparin
or other polysaccharides is done by suitable chemical treatments. Moreover, unlike other polysaccharides, hyaluronic acid is only slightly sensitive to the partial oxidation reactions, which allow reactive aldehyde-type groups to be introduced on this polysaccharide [59, 60].

This description demonstrates that there exists a clear need for new and improved thromboresistant, infection resistant and bioactive medical devices. This need can be met by devising an effective and inexpensive method whereby a stable chemical bond can be formed, simply and reliably, between the substrate and the polysaccharide, in such a way that the intrinsic characteristics can be exploited to the fullest extent possible.

One method using this approach involves the coating with a non-smudging biologically compatible hydrophobic crosslinked vinyl-containing silicon polymer coating material such as polymethyl vinyl siloxane or polymethyl phenyl vinyl siloxane. In this method, the coating material contains at least one optically compatible medicament which can be gradually and controllably released with time and which makes the lens suitable for implantation in both the phakic and aphakic eye [61].

To achieve biocompatibility using a similar approach, modification of solid surface involves a process in which a substrate having a surface which bears substrate pendant functional groups is biocompatibilized by coating it with a coating composition. The coating composition containing a polymer formed from a radical polymerizable zwitterionic monomer and a radical polymerizable monomer containing a reactive group to form a polymer having zwitterionic groups and pendant reactive groups. The pendant reactive groups are reacted to form covalent bonds with said substrate pendant functional group to form a stable coating of the polymer on the surface [62].

When the surface is hydrophilic and bears functional groups, then groups that are capable of reacting with surface functional groups to form covalent bonds may be used to bind the polymer to the surface. When the surface is charged then groups bearing ionic charge may be used to bind the polymer to the surface by ionic interaction [63].

The coating of the polymeric articles (e.g. IOL) with a substance, which is normally present in animal tissues e.g. hyaluronic acid, its derivatives or other natural or semi synthetic polymers or polysaccharides, has been found to be effective in increasing biocompatibility.

An interesting approach to the preparation of non-thrombogenic materials is the adsorption of heparin onto the surface of synthetic polymers, by using quaternary ammonium salts. In most cases, the main disadvantage of this method is a slow release of the quaternary ammonium salts into the blood stream. Further more, it is known that most compounds containing ammonium groups have hemolytic properties and may exert adverse effects on platelets [64]. This probably applies also to quaternary ammonium group-bearing surfaces.

Crosslinked poly(amoido-amines), besides being able to absorb heparin stably, show on the whole an excellent hemocompatibility. Consequently, they were good candidates for use in the biomedical field as heparinizable materials. A similar approach can be used for modifying surfaces consisting of hydrophobic materials having metallic, ceramic or glass surface so as to form a hydrophilic polymeric coating on the surface of an IOL [64].

For improving the problem of thrombogenicity, anti thrombic intraocular lenses were prepared by immobilizing a fibrinolytic substance on an intraocular lens surface.
It was found that the use of heparin in the irrigation solution reduces postoperative inflammation and cellular reaction as it reduces disturbances of the blood-aqueous barrier in the early postoperative period. It is known that heparin surfaces exhibit a high degree of biocompatibility in contact with blood and cell culture [64]. Modification of surface of IOL with heparin can increase biocompatibility. Many combinations with heparin were also studied so that one can reach a desired level of biocompatibility. People have tried albumin and heparin multilayer coatings for blood contacting medical devices [65].

Heparin sulphate is a very powerful anticoagulant in the natural vasculature. Consequently, it has been of great interest to physicians and the medical industry to devise blood contacting polymeric surfaces that possess characteristics of heparin sulphate, specifically by coating surfaces with heparin. Carmeda Inc, Sweden has manufactured a heparin coated bioactive surface under the trademark ‘Carmeda Bioactive Surface’ (CBAS), in which an end point of the heparin molecule is covalently coupled to an underlying polymer matrix. It was noted from the work with heparinized stents and tubing that these devices resulted in improved biocompatibility due to the coating of surfaces in contact with biologically active tissues [66]. On the other hand, aqueous solutions of hyaluronic acid its salts and derivatives are characterized by notable viscosity, slipperiness, and ability to reduce friction. Surfaces treated with such materials are characterized by a high degree of wettability and are able to inhibit the adhesion of cells or bacteria present in the biological fluids [67]. Also an artificial surface modified with immobilized heparin or hyaluronate were evaluated as possible approaches to improve biocompatibility.

A wide variety of methods have been developed till date to coat device surfaces to provide them with desired characteristics of biocompatibility. However, Porssa et al. have discovered that the performance of heparin coated devices which are commercially available, as components of extra corporeal devices, deteriorates after short periods of use. It is not known whether this is due to the heparin being removed from the surface or due to the surface becoming fouled by components of blood or other biological liquids in contact with the surface during use, such that the heparin is masked [68].

It was observed that heparin-surface modified IOL are more advantageous than PMMA laser in young patients [69]. In diabetic patients, inflammatory cells are adhered to the exposed PMMA surface more than to the HSM surface. Marked decrease in fibrinous reaction in the eyes with heparin surface modified IOL was also found [70].

**Foldable Intraocular Lenses**

Foldable Intraocular lenses are based on two chemistries:

(a) Silicones and modified silicones

(b) Acrylics and modified acrylics

Since acrylics as described earlier are more preferred materials for IOLs, acrylic hydrophobic intraocular lenses are described in detail in this paper.

**Hydrophobic Acrylic Intraocular Lenses**

Hydrophobic acrylic IOL materials are crosslinked polymers or copolymers of acrylic esters. In addition to a major acrylic ester monomer, they include other acrylic or methacrylic ester co-monomers. They owe their excellent optical properties, chemical
stability, and physical properties to a saturated, all-carbon backbone and polar ester-containing side groups.

**Tab. 3.** Chemical and physical properties of hydrophobic acrylic IOLs.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>High refractive IOLs</th>
<th>Low refractive IOLs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemistry</td>
<td>Aromatic acrylate-methacrylate copolymer</td>
<td>Aliphatic acrylate-methacrylate and fluormethacrylate terpolymer</td>
</tr>
<tr>
<td>Composition</td>
<td>Pure acrylate-methacrylate copolymer</td>
<td>Fluorinated acrylate-methacrylate terpolymer</td>
</tr>
<tr>
<td>Refractive Index</td>
<td>1.55</td>
<td>1.47</td>
</tr>
<tr>
<td>Water contact angle</td>
<td>72 °</td>
<td>88 °</td>
</tr>
<tr>
<td>Size/Shape</td>
<td>Full size optic (5.5 mm, 6.0 mm and 6.5 mm)</td>
<td>Varying size optic (less than lens diameter) with constant center optic thickness</td>
</tr>
<tr>
<td>Product Range</td>
<td>Available as multi-piece and single piece lenses</td>
<td>Available only as multi-piece lens</td>
</tr>
<tr>
<td>UV Stabilizer</td>
<td>Benzotriazole UV Blocker</td>
<td>Benzophenone UV Blocker</td>
</tr>
<tr>
<td>Manufacturing technique</td>
<td>Manufactured using advanced direct lens optic casting technology</td>
<td>Manufactured using conventional lathe cut tumble-polishing technology</td>
</tr>
<tr>
<td>Biocompatibility</td>
<td>Satisfactory</td>
<td>Satisfactory</td>
</tr>
</tbody>
</table>

**Clinical Aspects of Hydrophobic Acrylic IOL**

The clinical success of an IOL depends not only on the lens material, but also on the design of the device. The capsular bag is a delicate environment with which the IOL must be compatible.

Factors that contribute to this biocompatibility rapidly evolved through clinical experiences with foldable IOLs during the 1990s. These experiences established that the IOL surface properties must be optimized to achieve the desired interfacial interactions with the capsular bag, and that physical attribute and biomechanics of the IOL facilitate biocompatibility and achieve the optical objectives of the implant. An ideal biocompatible foldable IOL is well accepted by the surrounding ocular tissues, is biocompatible with the capsular bag, and provides satisfactory visual acuity during the patient's lifetime without additional secondary surgical interventions [48]. Hydrophobic acrylic IOLs have been proven to be among the most biocompatible IOLs currently available.

The high refractive index family of IOLs is the hydrophobic acrylic lens with which cataract surgeons have the most experience. It was released to the market early in 1995 and was the only hydrophobic acrylic lens available until February 2000, when one low refractive index lens made of fluorinated acrylate and methacrylate terpolymer successfully gained FDA approval.
Before high refractive index lenses was released to the market, a study was performed at the Medical College of Georgia to investigate the interaction of this new IOL material to medications such as dexamethasone, pilocarpine, gentamycin, and norepinepherine [71]. The study demonstrated that these IOLs did not act as a reservoir for drugs that penetrate into the eye. The soft acrylic material has a glass transition temperature (T_g) of 11 °C, which allows it to be folded at operating room temperature and inserted through a small incision. The lens then unfolds slowly and gently as it warms inside the capsular bag. Early studies of acrylic IOLs investigated the possibility of damaging the IOL during the folding and insertion procedures and the effects this damage had on the optical quality of the device.

One study conducted in cooperation between the University of Tokyo and Chiba University assessed the effect of folding procedures on the modulation transfer function (MTF) and resolving power (RP) of the IOL [72]. The study concluded that the optical quality of the device was not easily affected unless extreme non-physiological manipulations were applied.

Another study conducted by the Center Saint Victor, Amiens Cedex, France, investigated the frequency and cause of scratches or marks on the IOL [73]. The investigator concluded that the acrylic IOL was more fragile than silicon IOLs, but that alteration caused by folding did not affect visual acuity. These early complications of marks and scratches created on the lens during folding and insertion was overcome with the advent of the Monarch I Injector and later, the Monarch II Injector. This device now facilitates the insertion of a high refractive index lens into the capsular bag through approximately a 3.0-mm to 3.2-mm incision and drastically decreases the possibility of damaging the material surface.

Additionally, in a recent study, Kei Muller-Jensen, MD, and Bjorn Barlinn, MD concluded that high refractive index lens implantation is useful for patients with spherical corneas because of avoidance of postoperative astigmatism [74].

Continued implantation of the device revealed the most notable attribute of the new acrylic IOL- the reduction of PCO. Tetsuro Oshika, MD, and colleagues reported less frequent PCO two years after surgery in 64 eyes with acrylic lenses [75]. Paul G. Ursell, MD and colleagues reported significantly reduced degrees of PCO with the acrylic lens, compared with silicone and PMMA lenses, two years postoperatively [76].

Emma J. Hollick, MD and colleagues reported significantly reduced PCO rates and lower YAG rates up to three years following implantation of polyacrylic lenses [77]. In another study, Dr. Hollick and colleagues demonstrated that the presence of LEC on the posterior capsule was considerably lower with polyacrylic IOLs than with PMMA or silicone IOLs, and also that LEC regression occurred more frequently [78]. The PCO rates for the high refractive index IOL is approximately 11%, whereas the PCO rates for other common silicone or PMMA lenses range from 35% to 65%.

Observations with regard to decreased capsule opacification associated with acrylic lenses are not limited to the posterior capsule. Liliana Werner, MD, and colleagues noted in a comparative autopsy tissue study involving a wide variety of IOL designs and materials that the incidence of Anterior Capsule Opacification (ACO) was least with acrylic lenses [79].

Another issue related to the anterior capsule concerns the stability of the relationship between the anterior capsule and the IOL. During the months following surgery, the
anterior capsule can contract and lead to capsular phimosis syndrome or retract and lead to decentration of optic or PCO.

Dr. Ursell and colleagues demonstrated that implantation of the high refractive index lens produces significantly less anterior capsule movement than PMMA or silicon lenses, and thus is likely to cause less decentration and capsular phimosis [80]. Low rates of PCO, ACO and a stable anterior capsule with regard to the IOL are characteristics of a biocompatible implant. Dr. Hollick and colleagues demonstrated this biocompatibility by comparing the macrophage foreign-body response seen on the acrylic IOL with that seen on the PMMA and silicone IOLs. The macrophage response consists of small fibroblast-like cells and giant cells. The investigators determined that the silicon IOL had significantly higher small cell than the PMMA and acrylic lenses, and that the acrylic lenses had significantly fewer giant cells than either the silicone or PMMA lenses. These results indicate that the high refractive index lens may produce good results in eyes with pre-existing blood-aqueous barrier damage [81].

Also, in their two year follow-up of patients, Dr. Oshika and colleagues that the aqueous flare intensity of eyes implanted with a soft acrylic IOL was less than that of eyes implanted with silicon or PMMA IOL. The investigators hypothesized that this was a result of the thinner profile of the high refractive index acrylic lens, as well as the adherence of the acrylic material of the capsular bag [75].

As observations concerning decreased incidences of PCO, ACO and increased indications of biocompatibility became commonplace in the industry, focus turned toward examining the details of the interaction between the acrylic IOL and the capsular bag. Reijo Linnola, MD derived a theory, which he termed the “sandwich theory” [72]. This theory states that biocompatible materials can be either bioinert or bioactive, and that bioactive materials are necessary for an IOL to prevent PCO.

A bioinert material does not bind to the LEC as they migrate and proliferate between the posterior capsule and IOL. A bioactive material, however, forms a bond with a single layer of LEC, which are also bound to the posterior capsule. The tight bonds between both the LEC and the posterior capsule and the LEC and the IOL prevent any further LEC migration behind the IOL. With only a single layer of LEC behind IOL, the visual axis remains clear. Over time, some of the cells in this single sandwiched layer die demonstrating a regression of LEC. A bioactive bond then forms directly between the IOL and the posterior capsule.

Dr. Linnola and colleagues continued to pursue this theory [82-86]. The roles of fibronectin, vitronectin, laminin, and collagen type IV in the adherence of hydrogel, PMMA, silicone and acrylic materials to LEC and the capsular bag were examined. The sandwich structure of IOL /1cell layer/ capsule was observed with a significantly higher incidence in association with the high refractive index IOLs, and fibronectin was identified as the extra-cellular protein involved in the formation of this structure.

Robert L. Johnston, MD and colleagues performed an in vitro study and demonstrated that PMMA bound significantly greater quantities of albumin than the acrylic material, and that the acrylic material bound significantly greater quantities of fibronectin [87].

In addition, Nagata and colleagues demonstrated in vitro that a collagen film, derived from an extract of cow skin and a biomaterial having properties similar to those of the lens capsule surface formed a stronger bond to the surface of a high refractive index IOL than a PMMA IOL [88].
Similarly, Dr. Oshika and colleagues performed both an in vitro study examining the adhesive force between a collagen film and the IOL surface and an in vivo rabbit study examining the adhesion of the IOL to the capsule 3 weeks following implantation. In both cases, the acrylic IOL demonstrated significantly higher adhesion force than the PMMA and silicone IOLs. The investigators concluded that these differences seemed to play a role in preventing LECs from migrating and forming PCO [89].

Another equally important characteristic of the high refractive index lens is the design of the device. These IOLs have a sharp, keen, rectangular edge design, whereas the edges of other common silicone and PMMA IOL are rounded.

Okihiro Nishi, MD, and colleagues investigated the effect that the shape of the high refractive index IOL edge had on creating decreased incidence of PCO. The study demonstrated that there was a discontinuous bend in the capsular bag at the edge of these IOLs, and this discontinuous bend inhibited the proliferation of LEC behind the IOL. The investigators concluded that the edge design of the high refractive index IOL is a significant contributing factor in decreasing PCO, and that acrylic material properties, such as the adhesiveness of the material to the capsular bag, also played a role in creating this discontinuous bend, and thereby, in decreasing PCO [90].

Recently, an additional design option for the high refractive index IOLs has been approved and introduced to the market. Rather than the traditional three-piece design, in which the PMMA haptics are attached to the acrylic optic, the lens is now also available as a one-piece, open loop design, in which the optic and haptics are a continuous structure fabricated out of the acrylic material. The soft acrylic haptics place significantly less stress on the capsular bag than PMMA haptics, and this low applied force is constant over time, showing no force decay. The design of the haptic elbow permits a broad area of haptic contact with the capsular bag under varying compression forces, allowing for increased bio-integration of the lens with the capsule. This newest advancement in the IOL industry is expected to have a significant effect in decreasing posterior capsule striae following cataract surgery. In addition to the recent renovations of the high refractive index hydrophobic, acrylic IOL, a new representative of this material class, containing fluorinated acrylate-methacrylate terpolymer, has been introduced to the market. During a clinical study, the Sensar IOL demonstrated good clinical performance characteristics. One-year postoperatively, 85 % best corrected distance visual acuity of 20/40 or better was reported, with 39 % of 20/20 or better [91].

Conclusions
From the review of the existing knowledge on various aspects of IOL presented in this paper, following conclusions can be drawn:

(a) There exist several possibilities to correct the vision of eyes starting from the use of spectacle lenses to contact lenses to IOL. For every type of requirement and limitation there is a remedy to offer.

(b) There exist advanced surgical techniques to correct the bio-medical deficiencies such as cataract, etc. The present day surgeons are capable of correcting the vision of the eyes with minimum possible insertion or discomfort to the patient.

(c) The developments of new techniques have become feasible, thanks to the availability of advanced materials with improved properties. However, the fact is that the need for better cheaper and biocompatible materials never ends.
(d) The chemistries explored so far provide leads to develop materials with a specific functionality as also with unique features to take care of the demands of a given application. In this context, the development of polymeric materials is a notable example. The conventional materials are being slowly but steadily replaced by polymeric materials.

(e) Polymeric materials with appropriate rheological behavior at different temperature ranges including the temperature of a human body have obviously become the materials of choice when it comes to implants of various types. Even though certain developments after World War II were accidental, their multiplying effects clubbed with multidimensional success stories have led to the development of various types of IOL based on different types of polymers.

(f) Understanding of the structure-property correlation in terms of the physico-mechanical properties such as glass transition temperature, wettability, flexibility, oxygen permeability etc., chemical properties such as stability, inertness etc. and biochemical properties such as biocompatibility has enabled the scientists to come up with materials with desired properties and behavior.

(g) Several ways have been tried to achieve biocompatibility taking advantages of different aspects of materials, for example, chemical composition and chemical modifications by creating new groups with essential attributes, manufacturing techniques to provide desired surface properties besides the comfortable size and shape of the device and surface modification with help of certain biocompatible coating materials.

(h) Efforts in all the directions are needed to meet the requirements.

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