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UV Stabilizers for Novel Acrylate base Intraocular Lens

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ABSTRACT:

This research article relates to implantable intraocular lenses (IOLs) that have particular combinations of UV absorbers for providing desirable light transmission characteristics. Numerous UV absorbers like benzotriazole, benzophenone, triazine, etc are known for their UV stabilization activity. These combinations of UV light absorbers in to the formulated acrylate monomers which polymerized by photopolymerization process, allow an ophthalmic device material designer, to provide a wide range of different light transmission cut-off curves and/or characteristics like high refractive index, low glass transition temperature, tensile strength and good optical quality to the implant device material depending upon the combination of novel acrylate monomers with relative amounts of UV light absorber that are used.

KEYWORD: Intraocular Lens, UV Absorber, Photopolymerization, refractive index, glass transition temperature (Tg), tensile strength.

INTRODUCTION:

The consequences of exposing the skin to ultraviolet (UV) radiation are well understood in the general population with 95% of people associating UV with skin problems and 85% knowing about the risk of skin melanoma[(1)]. This level of understanding is substantially different when it comes to the eye however, with only 7% of people associating UV with eye problems [(1)]. It has been said that aside from skin, the organ most susceptible to sunlight-induced damage is the eye [(2)]. Over time, the natural crystalline lens yellows and loses its transparency, primarily due to irreversible lens protein changes caused by aging, heredity and UV exposure[(4)]. Exposure to UV radiation has been shown to lead to the development of cataract in animal models [(5)] and the link between UV and cataract formation in humans is well established [(6, 7, 8)].

The natural crystalline lens absorbs both UVA and UVB. It is exposed to three times more UVA, but both types of radiation are known to damage the lens via different mechanisms. This is illustrated by the fact that UVB at 300nm is roughly 600 times more biologically effective at damaging ocular tissue than UVA at 325nm[(3)]. A significant positive correlation has been reported between UVB and cortical cataract; there is also a possible association with posterior sub-capsular cataract [(9, 10)].

Cataract lens can replaced by polymeric intraocular lens for re build the vision, but UV radiation in the range of 280-380 nm, which corresponds to 420-320 kJ, is responsible for polymer degradation. This energy is sufficient to break C-C, C-H, C-O, C-Cl, C-N covalent bonds, hence signifies the need of using light stabilizer in intraocular lens which is exposed to direct or indirect sun-light.

Generally UV stabilizer mix into the melt or into the polymer solution where the molecules of the stabilizer diffuse into the polymer or dissolve in it. In order to apply this method the stabilizers and the polymers must satisfy certain requirements. The stabilizer must be in a finely dispersed form in order to be able to diffuse or to dissolve into the polymer mass. The compounds have to be treated in advance by fine grinding to a definite size and mixed with other additives, facilitating the processes of diffusion.

The main disadvantage of this method is that the resulting polymer is a mixture of higher and lowers molecular fractions. The lower molecular substance (the stabilizer) may evaporate during the molding and extrusion processes and migrate to the surface of the polymer during storage and/or application. This can change some of the properties of the polymer. Besides, some widely applied polymers as polyesters and polyamides, due to the high density of their polymeric structure, have problems with this method of stabilization.

Novel IOL prepared using combination of hydrophobic and hydrophilic monomers along with UV stabilizers like benzophenone and benzotriazoles derivatives are reported in this article. In present article, monomeric formulation with different UV stabilizer in different concentrations was polymerized using photopolymerization process. Photopolymerization, in addition to its environmental friendly aspect, offers a number of advantages, such as ambient temperature operations, location and time control of the polymerization process and minimal heat production, in comparison with other techniques [11]. Photopolymerization can be induced by ultraviolet (100–400 nm), visible (400–700 nm) or infrared (780–20000 nm) radiation. Light quanta are absorbed by molecules via electronic excitation [12]. During photopolymerization process, photoinitiator are generally used having high absorption capacities at specific wavelengths of light thus enabling them to produce radically initiated species [13]. The effect of incorporation of such UV stabilizers in to IOL was evaluated for their performance with respect to UV stability and also its physico chemical properties. The added concentration and nature of the UV monomer has shown the significant effect on the UV cutoff, leachability, extractable, refractive index, tensile strength etc. on the resultant IOL.

MATERIAL AND METHOD

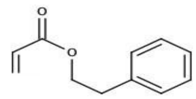
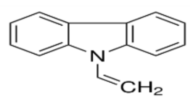
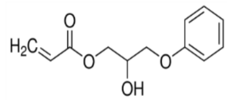
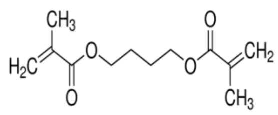
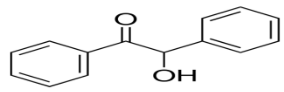
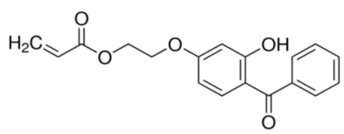
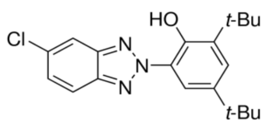
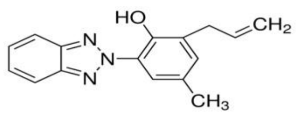
Material

All the monomers like 2-phenylethyl acrylate (PEA), 9-vinyl carbazole(VC) , 2-Hydroxy-3-Phenoxy propyl acylate (HPPA), 1,4-butanediol dimethacrylate (BDDMA), 2-Hydroxy-2-phenylacetophenone(HPA), 2-(4-Benzoyl-3-hydroxyphenoxy)ethyl acrylate (UV-1) , 2,4-Di-tert-butyl-6-(5-chloro-2H-benzotriazol-2-yl)phenol(UV-2) and 2-(2H-Benzotriazol-2-yl)-4-methyl-6-(2-propenyl)phenol (UV-3) were procured from Sigma-Aldrich and their chemical structures are presented in Table-1.

Method

The process of making IOL is basically a polymerization of the UV stabilized formulated mixture (UFM) solution which consists of monomers, UV absorber substances, crosslinker and initiators.

Table-1: Composition of formulated mixture (FM)

Monomer Name	Structure	Weigh (gm)
PEA		82
VC		10
HPPA		6
BDDMA		2
HPA		0.1
UV-1		Added as per Table-2
UV-2		Added as per Table-2
UV-3		Added as per Table-2

In present article all the monomers were mixed in the different proportion as described in Table-1. Such formulated monomeric mixture stirred continuously for about 3 hrs at room temperature it gets homogenized.

This formulated mixture (FM) is used further to make UV stabilized formulated mixture (UFM) using three different UV stabilizer in different concentration as described in Table-2. Before polymerization of UFM, the formulated mixture was then passed through the filter having pore size of 0.5 micron to remove the smallest size of the impurities in it.

Table-2: UV stabilized formulated mixture (UFM)

UV stabilizer		Product
Name	**Weigh added in FM (gm)**	**Code No.**
UV-1	0.1	UFM-1
	0.2	UFM-2
	0.4	UFM-3
UV-2	0.1	UFM-4
	0.2	UFM-5
	0.4	UFM-6
UV-3	0.1	UFM-7
	0.2	UFM-8
	0.4	UFM-9

The various UFM mixtures were filled in a polypropylene cup and sealed in an inert environment. All the formulated mixtures (UFM -1 to UFM-9) and formulated mixture without UV stabilizer (UFM-0) were polymerized under identical conditions by photo polymerization in UV chamber. Polymerization was carried out in UV chamber using 6 UVA lamps (centered at 350 nm) placed on top of the chamber with the distance to the sample 15 cm. Time of polymerization was 8 hours.

After completion of polymerization, polymerized disc remove from the mold and IOL cut from the polymeric disc in required geometrics with the help of CNC (computerized numerical control) machine. Evaluation of IOL done on the basis of its physico-chemical properties like UV cutoff, extractable, water absorption, refractive index, tensile strength, flexibility, foldability and surface quality. The methods adopted for analysis and the instruments used are described as follows.

Evaluation of IOL

UV cutoff

UV cutoff capacity of UV stabilizer incorporated IOLs compared with UV cutoff capacity of IOLs without UV stabilizer. The % of Transmittance and UV cutoff in region of 200nm to 800 nm was determined on the UV-Visible spectrophotometer (U1800) procured from Shimadzu.

Extractable

Quantitative determination of substances extractable from lenses was done by Soxhlet extraction method using different solvents as per ISO-18369-4. The lenses are dried to constant mass and the difference between the original dry mass of the lenses and the extracted dry mass determines the quantity of extractable substances (extractable).

The value Extractable (%) was calculated as per equation.

$$w_{\text{extracted}} = \frac{(m_1 - m_2)}{m_1} \times 100$$

Where,
m1 is the mass of lenses prior to extraction;
m2 is the mass of extracted lenses.

Water absorption

Water absorption was determined as per ASTM D792-08. IOLs were incubated at room temperature in water and evaluated after every 24 hour until they become fully saturated with water and there is no water absorption. The value of water absorption (%) was calculated as per equation.

Water absorption (%) = [(W2-W1) / W1] x 100

Where,
W1 = Weight of the sample before water absorption (in grams)
W2 = Weight of the sample after water absorption (in grams)

Refractive index

Refractive index was determined by using Abbe refractometer (ATAGO DR-A1) as per ASTM D542. Refractive index of material determine by as per following procedure.

1. Put the test specimen (Liquid/Polymeric strip form) on the presume surface.

2. By simply setting the boundary line of refraction at the cross hairs (see figure-1), this refractometer directly indicates a measurement

value together with the temperature on a digital display (see figure-2).

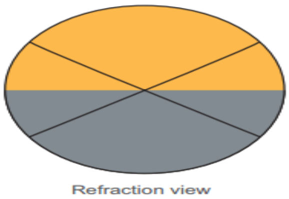


Figure-1 Refraction view of Refractometer

Figure-2 Display of Refractometer

Tensile strength

Tensile strength of intraocular lenses was determined as per ISO 11979-3 using Tensometer (Ametek-LLOYD LS-1). For determination of tensile strength, Clamp the optic so that the direction of pull is tangential to the loop at the loop/optic junction. After that set the extension rate in the range between 1 mm/min and 6 mm/min and activate the tensometer. Pull the IOL until the loop breaks or separates from the optic, or until the pull force reaches 0.25 N. Discard results if the loop breaks in the clamp.

Foldability and Flexibility

Foldability and Flexibility of the lenses were determined as per the following method:

The soft intraocular lens material in a dried state was folded into two at 25 ° C by means of tweezers and held in that state for 60 seconds, whereupon the folded state and the material was released, and the state at that time was evaluated in accordance with the following evaluation standards.

0. Very sticky, easily foldable but un-foldable after folding.
1. Foldable without exerting any extra force and unfolding time < 30 sec
2. Foldable with a slight force and unfolding time 30 to 60 sec
3. Foldable with extra force and unfolding time 30 to <180 sec
4. Cannot be folded and unfolding time > 180 sec

Optical Properties

Modulation transfer function (MTF) measurements using an eye model have become the internationally accepted standard for evaluating the performance of the image quality of an IOL. [14-18] The MTF of IOLs can be obtained using the International Organization for Standardization (ISO) standards [19-21] and an artificial eye. As per ISO-11979-2, the modulation transfer function (MTF) value of the system of model eye with IOL shall, at $100\ mm^{-1}$, should be greater or equal to 0.43.

Evaluation of in vitro glistening formulation in IOL

The presence of glistenings was measured by placement of a lens sample into a vial and adding deionized water or a balanced salt solution. The sample containing vial then placed into a water bath preheated to 45° C. Samples maintained in the bath for 48 hours. The sample is then placed either in a 37° C bath or at room temperature and allowed to equilibrate for 24 hours. The sample is removed from the vial and placed on a microscope slide. Visualization of glistenings is done on rapid-i vision measuring system using a magnification of 50 to 200×.

RESULTS AND DISCUSSION

The developed UV rays blocking intraocular lenses were evaluated on the basis their physico-chemical properties.

Best UV stabilizer along with its suitable concentration for making UV stabilized IOL was evaluated by comparing UV cutoff properties of all IOLs (i.e. UFM-0 to UFM-9) with each other which is shown in Table-3.

Table-3: UV cutoff properties of IOLs.

Product Code No	UV Cutoff (<10% Transmittance) at
UFM-0	<10% at 358nm
UFM-1	<10% at 362nm
UFM-2	<10% at 370nm
UFM-3	<10% at 372nm
UFM-4	<10% at 396nm
UFM-5	<10% at 398nm
UFM-6	<10% at 400nm
UFM-7	<10% at 398nm
UFM-8	<10% at 400nm
UFM-9	<10% at 402nm

As can be clearly seen from Table-3, UV-2 and UV-3 (i.e. UFM-4 to UFM-9) shows same UV cutoff capacity of IOLs. So, benzotriazole is the best UV stabilizer compared to benzophenone but as per shown in Table-4, foldability and flexibility of IOLs decreases with the increase the concentration of UV stabilizer.

Table-4: Foldability and Flexibility of IOL.

Product Code No	Foldability and Flexibility
UFM-0	1
UFM-1	1
UFM-2	2
UFM-3	2
UFM-4	1
UFM-5	1
UFM-6	2
UFM-7	1
UFM-8	1
UFM-9	2

Very sticky, easily foldable but un-foldable after folding.

1. Foldable without exerting any extra force and unfolding time < 30 sec
2. Foldable with a slight force and unfolding time 30 to 60 sec
3. Foldable with extra force and unfolding time 30 to <180 sec
4. Cannot be foldable

Foldability and Flexibility of the IOL play important role in cataract surgery. Hard lens create problem during transplantation of IOL and slow unfolding of IOL inside the chamber of eye can increase the chances of inflammation and infection in the eye after post cataract surgery. So from this point of view, among the all formulations product UFM-5 and UFM-8 were suitable for making UV rays blocking IOLs.

As per ISO-18369-4 guide line, % of extractable from the IOL must be at minimum level (preferably <0.8%). So, for this study UV incorporated IOLs (UFM-5 and UFM-8) were dried to constant mass and after completion of drying procedure IOLs was reflux for 9 hrs using Soxhlet assembly in methanol. IOLs were dried to constant mass and the difference between the original dry mass of the IOLs and the extracted dry mass of IOLs determines the quantity of extractable substances (extractable). The extractable of IOLs and after extractable its UV cutoff properties mentioned in following table-5.

Table-5: % of extractable and UV cutoff capacity of IOL before extractable and after extractable in methanol.

Product Code.	UV cutoff before Extractable	UV cutoff after Extractable	% of Extractable
UFM-5	<10% at 398nm	<10% at 366nm	0.98%
UFM-8	<10% at 400nm	<10% at 400nm	0.34%

As can be clearly seen from Table-5, UFM-8 (i.e. UV-3 with 0.2% concentration) was best IOL formulation for making UV rays blocking IOL. Even after extraction in methanol for 9 hrs, UV stabilizer not leaches out from the IOL. Although UV-2 and UV-3 are derivatives of benzotriazole, because of lacking of functional group in UV-2 which can help in further co-polymerization reaction, un-bounded UV-2 leach out in methanol but in the case of UV-3, it contains allyl group which can further co-polymerized with acrylate group. So co-polymerized UV-3 in IOL was not leach out in methanol from the IOL. As a result event after extractable, UV cutoff value of UFM-8 remains same (see figure- 3).

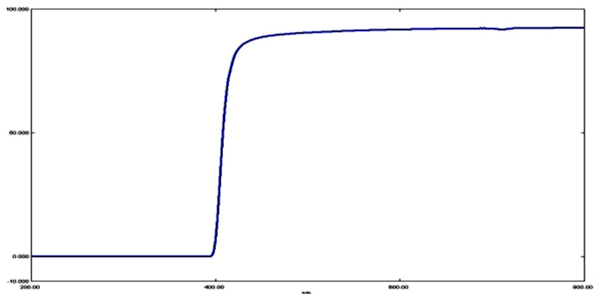


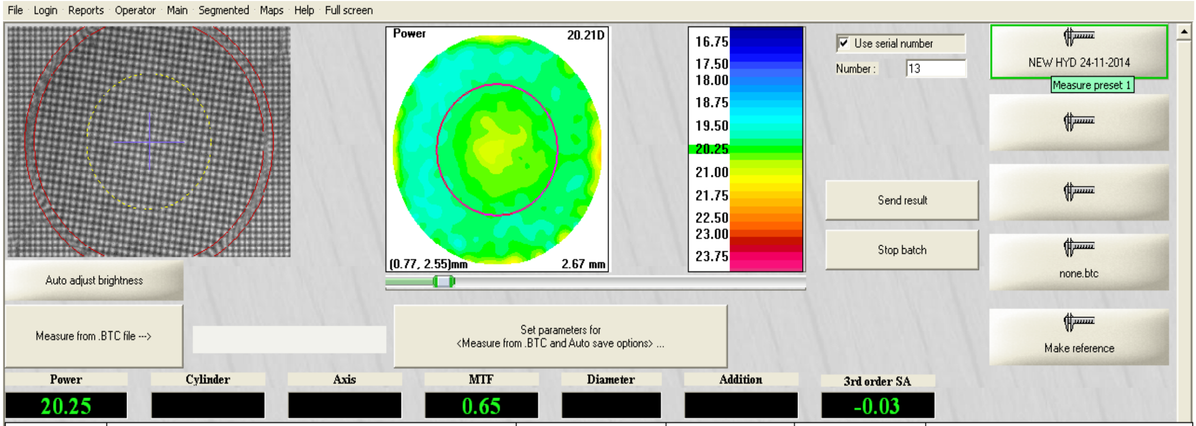
Figure-3: UV graph of UFM-8 IOL

Other Physico-chemical properties like refractive index, water content, tensile strength, glass transition temperature (Tg) and MTF value of UFM-8 IOL mentioned in Table-6.

Table-6: Physico-chemical properties of IOL.

Physico-chemical Properties of IOL	UFM-8 IOL
Refractive Index	1.57 at 25 °C
MTF Value	0.65
% of water content	0.23%
Tensile Strength	23.615 kgf/cm^2
Tg	9.62 °C

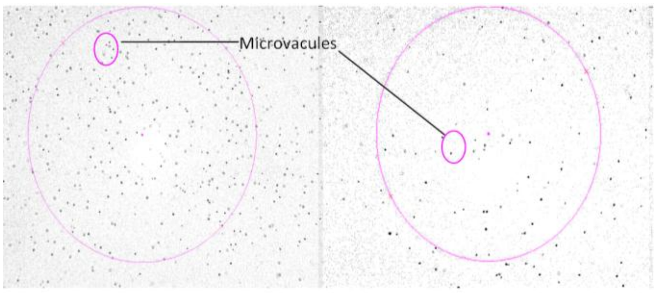
As can be seen from table-6, refractive index value of IOL is very high. High RI value makes the lens focus more sensitive to shape change from muscle's adjustment. Moreover, high RI lens materials can be cut thinner, providing a higher refractive power and reducing the friction between lens and iris. This will therefore improve biocompatible of lens in eyes especially for certain patients requiring this increase in add power as a result of their refraction (e.g. high myopia) and corneal curvature values. MTF value of the UV stabilized IOL is 0.65 (see Figure-4). It means IOL optical quality is very good.



Test Name	: Power Check and Imaging Quality		Standard	: ISO-11979-2	Test Name	Limit
DATE	BATCH NUMBER	STYLE	Label Clam Power	Check By sign	Power	± 0.25
22/10/2016	PNC3CSK03301	AS-6Y	20.00 D		Imaging Quality	Be greater or equal to 0.43 MTF value

Figure-4: MTF value of UV stabilized IOL

UFM-8 IOL also has sufficient water content which gives beneficiary effect on glistening. Generally glistening is the most common problem in hydrophobic IOL. In present article developed novel IOL from the combination of hydrophobic and hydrophilic monomers which also maintain the influx of the water in the IOL. This property hides the visualization of glistening without effect on refractive index of IOL. Glistening image of IOLs is as Figure-5.



Alcone IOL **UFM-8 IOL**

Figure-5: Glistening in IOL

The intraocular lens, which includes a portion termed the "optic", and supporting legs or loops termed "haptics", is introduced into in the eye through a small incision and then appropriately positioned within the eye itself.

For example, to place a lens in the posterior chamber of the eye, where the lens has an inferior and superior haptic, the inferior haptic is first passed through the pupil and into the posterior chamber. The superior haptic is then grasped with a suitable instrument and compressed or bent to a position close to the optic and pushed into the posterior chamber with the optic while held in this compressed position. Thereafter, the superior haptic is released and the lens is then finally positioned, to be held in place by engagement of the haptics with the eye tissue.

Thus it will be seen that flexibility and resiliency of the haptics is desirable to facilitate at least the described type of implantation of the intraocular lens.

As per ISO-11979-3, tensile strength (or loop pull strength) limit is greater than or equal to 12 kgf/cm^2. Tensile strength of UFM-8 IOL is 23.615 kgf/cm^2 (see Figure-6).

As can be clearly seen from Table-6, glass transition temperature (Tg) of UFM-8 IOL is very low i.e. 9.62 °C (see Figure-7). Such low Tg facilitate manipulation such as flexing and rolling of IOL during the surgical procedure even at lower operating room temperatures.

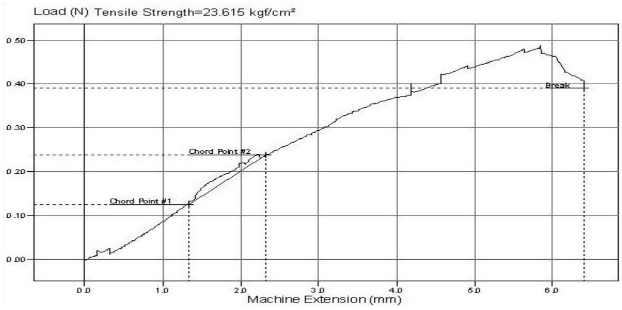


Figure-6: Tensile strength Graph

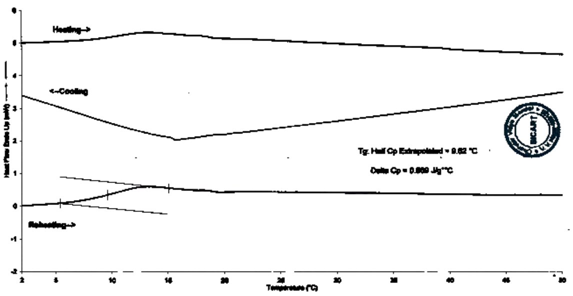


Figure-7: DSC Graph

CONCLUSIONS

Copolymeric materials containing combination of 82% PEA, 10% VC, 6% HPPA and 0.2% UV-3 stabilizer present good UV rays blocking capacity (<10% transmittance at 400nm), high refractive index values (1.57), good mechanical strength (23.615 kgf/cm^2), low glass transition temperature (9.62 °C), and good optical properties (MTF=0.65) for the fabrication of foldable intraocular lenses. These materials can be considered as a good alternative to the currently used foldable intraocular lenses.

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