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Drug Eluting Intraocular Lens

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ABSTRACT:

The aim of the current study is to design and characterize sustain antibiotic release intraocular lens (IOL) using a fourth generation fluoroquinolone antibiotic, Moxifloxacin hydrochloride for availability of antibiotics immediately in postoperative period after cataract surgery. Different novel acrylate base monomers with the combination of Moxifloxacin hydrochloride formulated for the synthesis of such type of IOL. The prepared IOL were evaluated for surface quality (MTF value), refractive index, extractable, tensile strength, in vitro drug release studies and microbiological studies. The selected IOL showed sustained release for the period of 7-week thus showing increased residence and contact time with eye. All studies showed favorable results thus drug eluting IOL system can be considered as alternative for conventional ophthalmic drops.

KEYWORDS: Intraocular lens (IOL); Fluoroquinolone; Moxifloxacin Hydrochloride; refractive index; Tensile strength; microbiological study.

INTRODUCTION:

The only treatment for cataracts is surgical removal of the cataract and its replacement with a synthetic intraocular lens (IOL). Although cataract surgery is remarkably successful in restoring the patients' vision, it still has potential risks of severe postoperative intraocular infection (such as bacterial endophthalmitis) that may result in devastating permanent vision loss. Endophthalmitis is an inflammation of the inner structure of the eyeball i.e., uveal tissue & retina associated with pouring of exudates in the vitreous cavity, anterior chamber & posterior chamber.Post-operative endophthalmitis is the most common form. It comprises 70% of infective endophthalmitis. Post operative Endophthalmitis (POE) is defined as a severe inflammation involving both the anterior and posterior segments of the eye secondary to an infectious agent. Postoperative endophthalmitis has been reported for every type of ocular surgery but cataract surgery is the most commonly performed type of ocular surgery.

The incidence of endophthalmitis has been reported to be between 0.13% and 0.7%.[(1)] The primary source of this intraocular infection is considered to be bacteria from the patient's ocular surface (cornea, conjunctiva) or adnexa (lacrimal glands, eyelids, and extraocular muscles).[(2)] The bacteria most frequently isolated are gram-positive coagulase-negative cocci (mainly Staphylococcus epidermidis) which account for 70% of culture-positive cases.[(2)] Staphylococcus aureus is isolated in 10% of culture-positive cases, Streptococcus species in 9%, Enterococcus species in 2%, and other gram-positive species in 3% of cases.[(1)] Gram-negative bacteria account for just 6% of culture-positive cases; however, an infection with these bacteria, particularly with Pseudomonas aeruginosa, can lead to a devastating visual outcome.[(1,3)]

The current standard postcataract surgery management requires the use of topical antibiotics (typically fluoroquinolone) as a prophylaxis against bacterial intraocular infection. Topical application of

antibiotics has a low level of intraocular penetration (<0.3%).

This requires higher concentration of topical applications to achieve the minimum inhibitory concentration (MIC) of the antibiotics within the eye [4]. Topical application of the antibiotic is costly and can result in toxicity of the ocular surface. Furthermore, it depends on the patients' compliance, which may be difficult in elderly population and developing nations. Therefore in the current research study a novel polymeric system was designed for sustained, rate-controlled release of sufficient intraocular antibiotics during the immediate postoperative period after cataract surgery.

The antibiotic chosen as a drug model for this study is a broad spectrum fluoroquinolone, Moxifloxacin HCL. Moxifloxacin hydrochloride is a synthetic broad spectrum antibacterial agent. It is a slightly yellow to yellow crystalline substance with a molecular weight of 437.9. Its empirical formula is C21H24FN3O4 *HCL. Moxifloxacin differs from other quinolones in that it has a methoxy function at the 8- position, and an S,S – configured diazabicyclononyl ring moiety at the 7-position. Moxifloxacin is a broad-spectrum antibiotic that is active against both Gram-positive and Gram-negative bacteria. It functions by inhibiting DNA gyrase, a type II topoisomerase, and topoisomerase IV, enzymes necessary to separate bacterial DNA, thereby inhibiting cell replication.

It has a spectrum of activity encompassing gram-positive and gram-negative bacteria, including S epidermidis, S aureus, S pneumoniae, S pyogenes, H influenzae, E coli, Bacillus cereus, N gonorrhoeae, and P mirabilis. Additionally, the fourth-generation fluoroquinolones have good activity against atypical pathogens such as Mycoplasma, Legionella, and Chlamydia species, as well as the anaerobic organism P acnes [5, 6].

The in vitro minimum inhibitory concentration to inhibit 90% of organisms (MIC90) of moxifloxacin to organisms commonly encountered in postoperative, post-traumatic, and bleb-associated endophthalmitis is low which is shown in Table-1.

In the current study different polymeric formulations were used in which moxifloxacin HCL drug incorporated and polymerized by UV polymerization to yield optically transparent intraocular lens material. Optimized composition and processing parameters were finalized based on the evaluation of polymers for surface quality (MTF value), refractive index, extractable, tensile strength, in vitro drug release studies and microbiological studies.

MATERIAL AND METHOD

Material

Moxifloxacin HCL was procured from TCI chemicals. All the monomers like 2-Hydroxy ethyl acrylate (HEA), 2-Hydroxy ethyl methacrylate (HEMA), Methyl methacrylate (MMA), Ethylene glycol diacrylate (EGDA), and 2-Hydroxy-2-phenylacetophenone (HPA) were procured from Sigma-Aldrich and their chemical structures are presented in Table-2

Method

The process of making Moxi (Moxifloxacin HCL) loaded IOL is basically a polymerization of the formulated mixture solution which consists of monomers, crosslinker, initiators and antibiotic drug Moxifloxacin HCL.

In the studies all the monomers and drug were mixed in the different proportion as described in Table-2. Such formulated monomeric mixture sonicated for 1hr and 30 minutes at room temperature for proper mixing of drug in to the monomeric solution. 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. Three different monomeric mixtures were filled in a polypropylene cup and sealed in an inert environment. All the formulated mixtures 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 it's physico-chemical properties like UV cutoff, extractable, water absorption, refractive index, tensile strength, flexibility, foldability and surface quality.

Table-1: MIC90 of Moxifloxacin , Levofloxacin, Ofloxacin and ciprofloxacin to organism commonly encountered in endophthalmitis.

Organisms	MIC90 VALUES (µg/mL)			
	Moxifloxacin	Levofloxacin	Ofloxacin	Ciprofloxacin
Gram-positive organisms				
Staphylococcus epidermidis	0.13 to 2.0	0.50	0.50	1.00
Staphylococcus aureus	0.06 to 2.0	0.25	0.50	0.50
Streptococcus pneumoniae	0.06 to 0.25	2.00	2.00	2.00
Streptococcus pyogenes	0.25	1.00	2.00	1.00
Bacillus cereus	0.13	-	0.50	-
Enterococcus faecalis	1.00	2.00	4.00	4.00
Gram-Negative Bacteria				
Proteus mirabilis	0.025	0.25	0.125	0.06
Pseudomonas aeroginosa	0.5 to 8.0	32.0	4.00	8.00
Haemophilus influenzae	0.03 to 0.06	0.06	4.00	0.016
Enterobacter species	0.06	-	-	-
Escherichia coli	0.06 to 1.0	0.03	0.125	0.016
Klebsiella pneumoniae	0.12 to 0.25	0.13	0.50	0.06
Neisseria gonorrhoeae	0.015	0.016	-	0.008
Anaerobic Bacteria				
Bacteriodes fragilis	0.125 to 2.00	2.00	-	8.00
Clostridium species	0.50 to 0.10	-	-	-
Propionibacterium acnes	0.032 to 0.25	-	-	-

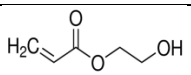
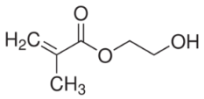
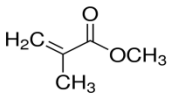
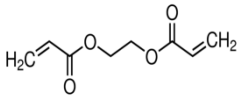
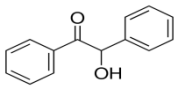
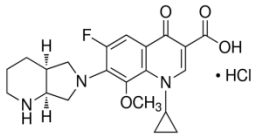
*MIC90 data are from Bauernfeind [7] and Osato et al.[8]. MIC90 data for Moxifloxacin are from references [9-11]

Evaluation of IOL

Preparation of standard stock solutions and calibration curve of Moxifloxacine HCL for in vitro Drug release study

The standard stock solutions of MOX was prepared by dissolving 50mg of drug in 10mL distilled water in 100mL volumetric flask, final volume was adjusted with distilled water to get 500 µg/mL. Working standard solutions were scanned in the entire UV range of 400-200 nm to obtain the absorbance spectra. The drug shows maximum absorption at 294nm. Nine working standard solutions of drug having concentration 0.5, 1, 2, 3, 4, 5, 10, 20 and 30 µg/mL were prepared in distilled water from stock solution.

Table-2: Formulations for Drug loaded IOL

Monomer Name	Structure	Formulation A Gm	B Gm	C Gm
HEA		45	50	70
HEMA		40	40	25
MMA		14	9	4
EGDA		0.4	0.4	0.4
HPA		0.1	0.1	0.1
Moxifloxacin HCL		0.5	0.5	0.5

Determination of Moxifloxacin HCL MIC90 against Staphylococcus Epidermidis

MIC90 of Moxifloxacin HCL against Staphylococcus Epidermidis (ATCC 12228) was determined by broth dilution method. Methodology used for this study was as follow. The organisms (Gram-positive Staphylococcus epidermidis) to be sub cultured using a Mueller Hinton Agar separately under optimal incubation conditions(at 37 °C for 24 hrs) to obtain a fresh overnight grown culture. A number of pure colonies (app. 5) were introduced into a glass culture tube containing Mueller Hinton Broth and incubated at 37°C overnight (or longer until clear visible growth is observed).Overnight grown culture tubes compared with 0.5 McFarland standard and standardized by diluting with sterile Muller Hinton Broth. Antibiotic concentrations 0.125, 0.25, 0.5, 1, 2, 4, 6, 8, 10, 12, 16 and 20 PPM were prepared in sterile distilled water. Following the preparation of the different concentration of antibiotic, 2 ml of freshly standardized broth culture of the strain was inoculated in each tube

according to the scheme outlined in Table-3 and mixed well before incubated aerobically at 37°C for 24h. The end-point was defined as the lowest antibiotic concentration for which there was no visual growth.

Table-3: Preparation of culture dilution series

MIC no	Volume of Antibiotic solution	Volume of broth culture	Final concentration
1	2 ml(20 PPM)	2 ml	**10 PPM**
2	2 ml(16 PPM)	2 ml	**8 PPM**
3	2 ml(12 PPM)	2 ml	**6 PPM**
4	2 ml(10 PPM)	2 ml	**5 PPM**
5	2 ml(8 PPM)	2 ml	**4 PPM**
6	2 ml(6 PPM)	2 ml	**3 PPM**
7	2 ml(4 PPM)	2 ml	**2 PPM**
8	2 ml(2 PPM)	2 ml	**1 PPM**
9	2 ml(1 PPM)	2 ml	**0.5 PPM**
10	2 ml(0.5 PPM)	2 ml	**0.25 PPM**
11	2 ml(0.25 PPM)	2 ml	**0.125 PPM**
12	2 ml(0.125 PPM)	2 ml	**0.0625 PPM**

In Vitro Drug Release study

In vitro drug release from drug loaded IOLs were investigated in ultrapure water. IOLs from each formulation were suspended in respective vials with 20 ml of ultrapure water and placed on a shaker at 100 rpm at 37 °C procured from DBK-instruments, Mumbai. The amount of drug released was determined by withdrawing 3 ml aliquots at the selected specific time intervals. The volume withdrawn was replenished with an equal volume of fresh and pre-warmed ultrapure water at 37 °C. Samples were analyzed by UV spectrophotometer (UV-1800 PC, Shimadzu,) at λmax value of 294 nm using ultrapure water as the blank.

Antimicrobial activity of MOX-loaded IOL

The antimicrobial efficacy of the Moxifloxacine HCL loaded IOL was evaluated against a Gram-positive microorganism Staphylococcus Epidermidis (ATCC 12228).

Muller Hinton agar media was poured aseptically into sterilized Petri plates, seeded with micro-organism (100 µL) and left to solidify. Cups were made by using sterilized stainless steel cup borer (4 mm diameter) and filled with 100 µL aliquots collected from in vitro release study of MOX-loaded IOL at different time intervals.

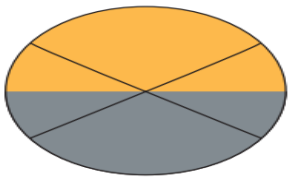
After inoculation of samples, plates were left at room temperature to diffuse the samples. Finally, plates were then incubated for 48 h at 37 ± 0.5°C. The diameter (mm) of the zone of growth inhibition was measured using a vernier caliper.

MTF Value

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. [12-16] The MTF of IOLs can be obtained using the International Organization for Standardization (ISO) standards [17-19] 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. This procedure was performed as per mentioned in ISO-11979-2 (annex C).

Refractive index

Refractive index was determined by using Abbe refractometer (ATAGO DR-A1) as per ASTM D542. Refractive index of material determine by (1^{st}).Put the test specimen (Liquid/Polymeric strip form) on the presume surface. (2^{nd}).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).



Refraction view

Figure-1 Refraction view of Refractometer

Display

Figure-2 Display of Refractometer

Water absorption and Extractable

Water absorption and extractable was determined as per ASTM D792-08. Initial weight of IOLs were measured before incubate in the water. After that 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. Water saturated IOLs were re-dried for calculation of extractable. The value of water absorption (%) was calculated as per following 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)

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

Extractable (%) = [(W1-W3) / W3] x 100

Where,
W1 = Weight of the sample before water absorption (in grams)
W3 = Weight of the sample after drying of hydrated sample (in grams)

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.

RESULTS AND DISCUSSION

Before evaluation of moxi-loaded three different formulated IOL, the calibration curve of Moxifloxacin-hcl was prepared for proper estimation of in vitro drug release from moxi-loaded three different formulated IOLs in the water. Working standard solutions were scanned in the entire UV range of 400-200 nm. Drug shows maximum absorption at 294nm and obtained absorbance spectra was as shown in figure-3.

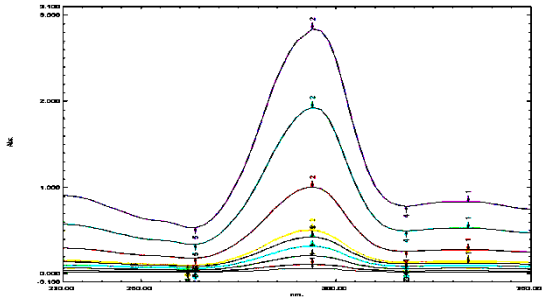


Figure-3: Absorbance Spectra of Moxifloxacin.HCL

Calibration curve of nine working standard (i.e. 0.5, 1, 2, 3, 4, 5, 10, 20 and 30 µg/mL) was as shown in Figure-4.

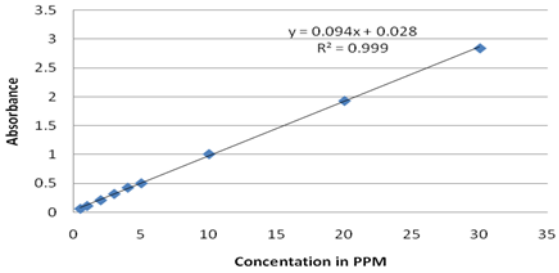


Figure-4: Calibration Curve

Moxifloxacin HCL MIC90 against Staphylococcus Epidermidis

Fresh overnight grown culture of staphylococcus epidermidis (ATCC 12228) shown in figure-5, prepared for determination of MIC90 of moxifloxacin.hcl. 5 colonies introduced into a glass culture tube containing Mueller Hinton Broth and incubated at 37°C overnight (or longer until clear visible growth is observed). Transmittance and absorbance of the overnight grown culture tubes can be easily compared with 0.5 McFarland standard and standardized by diluting with sterile Muller Hinton Broth.

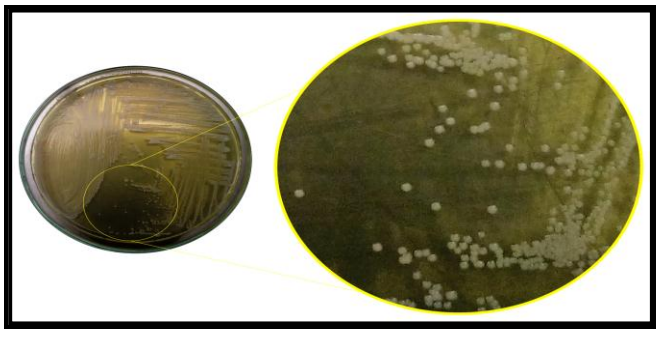


Figure-5: staphylococcus epidermidis colony

Antibiotic Concentrations and culture dilution series were prepares as discuss in material and method. The lowest antibiotic concentration for which there was no visual growth observed was 0.25 PPM, which was clearly seen in following figure-6.

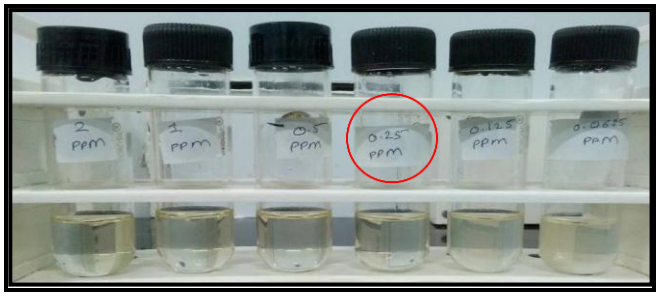


Figure-6: MIC90 Tube

In Vitro Drug Release study

The in vitro releases of moxifloxacin.hcl from IOLs constructs with different formulations were determined over a 7-week period. The peak absorbance was measured at various time points, and the cumulative mass of drug released was calculated and plotted as a function of time as shown in Figure-7.

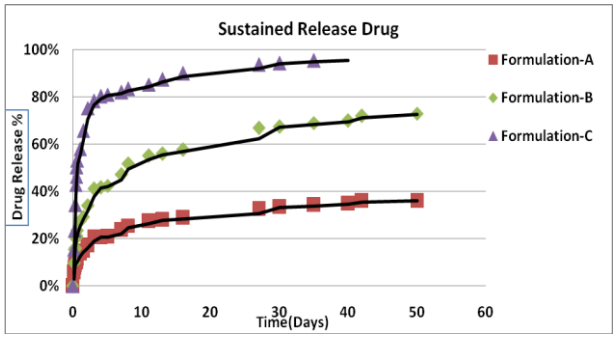


Figure-7: Sustain release drug graph

In the formulation-C, an initial burst release is seen, which is typical of IOL-based drug-delivery systems. [20, 21] A rapid glass-to-rubber transition occurs as water penetrates into the dehydrated IOL, resulting in the increased movement of the cross-linked polymer chains and accordingly, the diffusion of the loaded drug out of the matrix [22].

However, the addition of the MMA, acted as a rate-limiting barrier that delayed the imbibitions of water into the antibiotic-loaded IOL matrix, while simultaneously preventing the diffusion of the trapped antibiotic molecules out of the IOL [23]. The Formulation-B IOL showed that it can control the further influx of water and allowed for antibiotic release above the MIC, while release from the longer coated samples was below the lethal dosage. These findings demonstrate that the formulation-B IOLs are capable of delivering a clinically relevant dose of drug in situ over the critical 7-week postoperative period.

Antimicrobial activity of MOX-loaded IOL

Antimicrobial activity of Mox-loaded IOL (Formulation-B IOL) was compared with standard 0.25 PPM (MIC90 concentration) Moxifloxacin solution against Gram-positive staphylococcus epidermidis bacteria by cup plate technique. Zone of inhibition was used as an assessment parameter.

Zone of inhibitions for standard Moxifloxacin solution (MIC90 concentration) and Mox-loaded IOL were found to be 16.75 ± 0.65 and 17.56 ± 0.83 mm, respectively (Figure-8). In vitro release samples from Mox-loaded IOL showed the inhibition of growth of S. epidermidis throughout the test period, confirming the antimicrobial activity of the Mox-loaded IOL.

Figure-8: Zone of Inhibition

Other Physico-chemical properties like MTF value, refractive index, water content, extractable, UV cutoff and tensile strength of Mox-loaded IOL (Formulation-B) mentioned in Table-4.

Table-4: Physico-chemical Properties of Mox-loaded IOL

Physico-chemical Properties of IOL	Mox-loaded IOL
MTF Value	0.55
Refractive Index	1.461
% of water content	32.56%
% of Extractable	0.56%
Tensile strength	25.042

As can be clearly seen from table-4, refractive index value of hydrated mox-loaded IOL is 1.461. That much RI of lens materials can be cut thinner, providing a higher refractive power and reducing the friction between lens and iris. MTF value of Moxi-loaded IOL is 0.55 (see Figure-9). It

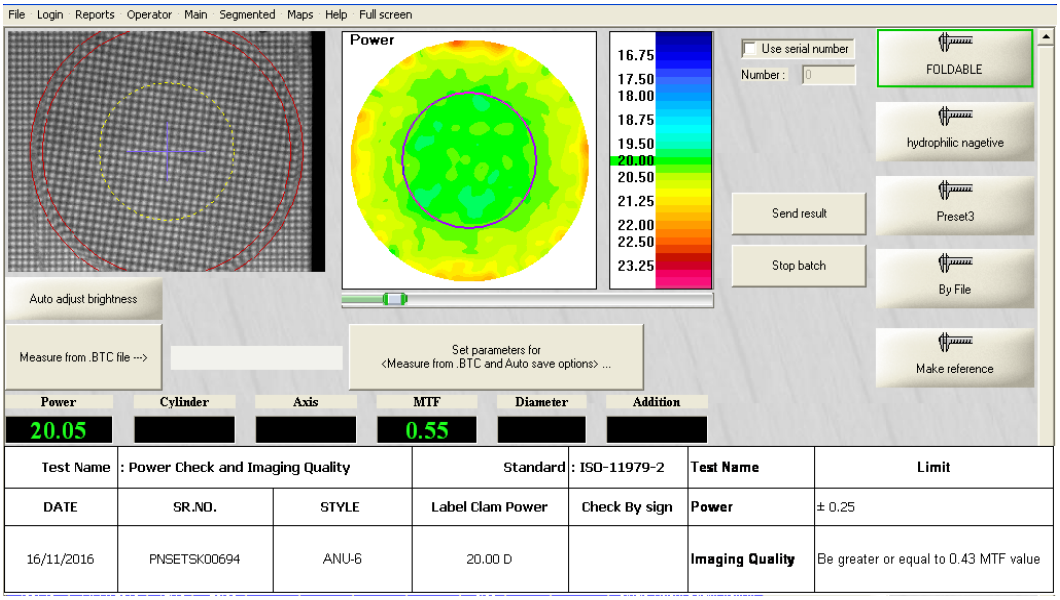


Figure-9: MTF Vale of IOL

means IOL optical quality is very good. Water content and extractable studies performed using drug free IOL (Formulation-B without moxifloxacin) for proper extractable results.

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 Mox-loaded IOL (Hydrated) is 25.042 kgf/cm^2 (see Figure-10).

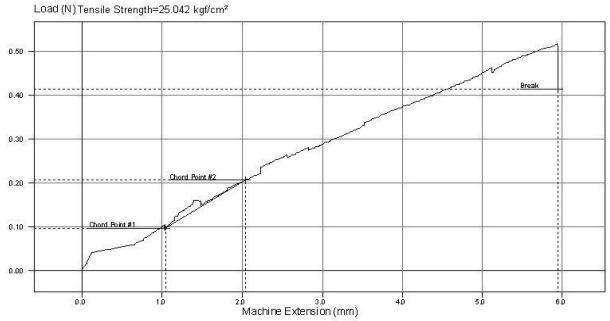


Figure-10: Tensile strength grap

CONCLUSIONS

The developed polymeric drug-delivery device delivered therapeutically effective antibiotics in the eye. The Mox-loaded IOL also have good phisico-chemical properties like good surface quality, refractive index value, less extractable vale, required water content value and good tensile strength. Because the antibiotics are released inside the eye (where the infection is most difficult to treat), The prepared device showed superior outcomes in controlling intraocular infection than conventional topical antibiotic drops. These drug-loaded intraocular lenses can be considered as a good alternative to the currently used foldable intraocular lenses.

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