Monomer's Residuals Test Elimination for Soft Acrylic Buttons at Polytechnic University of Puerto Rico

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Abstract *— In the cataract surgery, the natural lens in the eye is replace with an Intraocular Lens. Five monomers (EA/EMA, TFEMA, EGDMA, UV Chr) are mixed to produce the soft acrylic lens. Residual monomer testing measures the amount of monomer and crosslinker not polymerized or removed by annealing process. During the last years residual monomer testing become a high-cost test due to equipment maintenance, chemical purchases, and spare parts cost. Historical data was collected from the residual testing for Optiblue from January 2019 up to May 2020 and Opal from June 2018 up to May 2020. DMAIC methodology was used in this analysis. Process Performance Index (Ppk) value varies from 5.62 to 49.52 for Opal and 2.09 to 30.00 for Optiblue, which confirm annealing process is a capable and is in statistically control. Trend analysis was performed, and no negative trend was observed. Therefore, the monomer residual test can be eliminated.*

Key Terms *— Residual Monomer Testing, Opal, Optiblue, Process Performance Index.*

INTRODUCTION

Cataract is a cloud that cover the normal clear lens in the eye affecting the visibility of the person. This cloud is produced as result of tissue breakdown and protein clumping. During the cataract surgery, the natural lens in the eye is replace with an Intraocular Lens (IOLs) [1]. Medical devises companies that produce IOLs are focused in develop a large variety of IOLs such as refractive IOLs, Torics, Monofocals, Multifocals among others.

Sheet Casting Process is the first step in the soft acrylic lens generation process. There are two types of castings or lens model: Opal (clear buttons), and Optiblue (yellow buttons) Soft Acrylic Sheets. The Soft Acrylic Button is a cross-linked multi-constituent polymer used to produce Acrylic IOLs. Five (5) monomers (EA/EMA, TFEMA, EGDMA, UV Chr) are mixed to produce the soft acrylic lens (Opal). The Optiblue contain the same 5 monomers of Opal and additionally two (2) more additives (Yellow Dye, UVAM) to add the Ultraviolet (UV) blocker.

The process steps to receive and release the Soft Acrylic lens materials are as follows: The raw materials are purchased from approved suppliers. Monomers are processed using chromatography column to remove the inhibitor. Purity standards for each monomer are verified by either gas chromatography (GC) analysis or high-performance liquid chromatography (HPLC) analysis as applicable by procedures.

Once the materials are released to Production, the monomers are mixed and thermally polymerized in sheet form by means of Crystal Plates, using a curing bath and curing oven. Buttons are punched from sheets using a hydraulic press and annealed using a vacuum oven. Annealing is the stage of the process that removes any polymerization remaining material (monomer residual).

Release testing of the buttons includes Fourier transform infrared spectroscopy (FTIR), percent transmittance by ultraviolet – visible (UV/Vis) spectroscopy, residual monomer levels by HPLC, uHPLC or UPLC and Refractive Index (RI). The residual monomer levels testing measures the amount of monomer and crosslinker not polymerized or removed by annealing process.

METHODOLOGY

DMAIC methodology will be used for this analysis [2]. In the measure phase, residual results from January 2019 to May 2020 were evaluated for Optiblue and for Opal residual results were evaluated from June 2018 to May 2020.

The sampling size was determined using data previously collected and analyzed using Minitab Power and Sample Size technique, assigned a 0.5 of standard deviation for the difference, and 95% for confidence interval (CI). The historical data used for Power and Sampling Size analysis was Optiblue, based on test failures. The sampling size according to the Power and Sampling size analysis was 105. A total of 2,037 samples points was collected. Each PO consist of 5 sheets for Optiblue buttons and 16 sheets for Opal buttons.

A process capability analysis was performed using Minitab 18 to analyze the gathered data. The Process Performance Index (Ppk) was determined using Process Sigma and Yield for the 5 main monomers (EA/EMA, TFEMA, EGDMA, UV Chr), a Process Capability were analyzed to compare Process Performance Index (Ppk). Additionally, a trend analysis was performed to analyze any negative trend. It is important to highlight that EA/EMA is analyzed using the average of the residuals obtained from both monomers as established in the procedure and in the corresponding method validation.

RESULTS AND DISCUSSION

For the analyze phase, process capability analysis was performed using Minitab 18 to analyze the historical data collected from January 2019 to May 2020 for Optiblue, Opal from June 2018 to May 2020 was evaluated [4]. For sampling size, a Power and Sampling size technique was used with a 95% of Confidence level, and 0.5 of standard deviation of the historical data for the difference.

In Figure 1 the Sample Size of 105 is the closer to Power of 95%, therefore it was selected to analyze the data for this study. The assumed standard deviation was obtained from historical data [3].

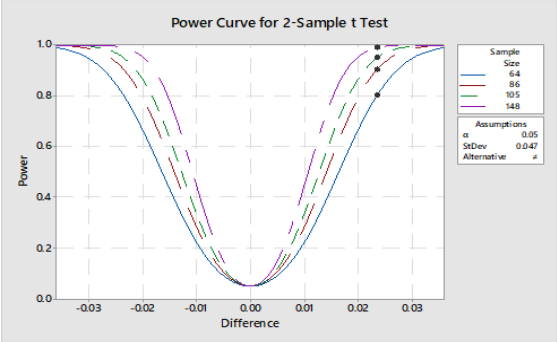
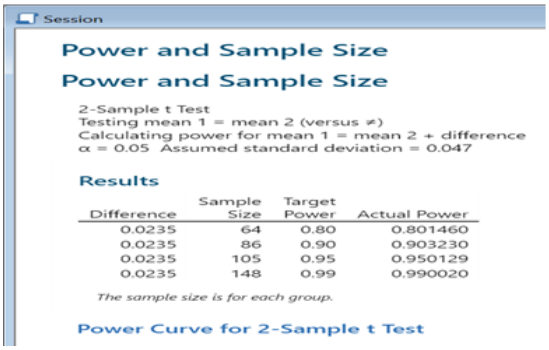


Figure 1
Power and Sample Size Analysis

In the Figure 2 it can be seen the Power and Sampling Size graph were four (4) different options of sampling size can be selected. For this study the sampling size of 105 was selected in order to detect any small deviations in the samples and it is the sampling that is closer to Power of 95%.


Session

Power and Sample Size

Power and Sample Size

2-Sample t Test
Testing mean 1 = mean 2 (versus ≠)
Calculating power for mean 1 = mean 2 + difference
α = 0.05 Assumed standard deviation = 0.047

Results

Difference	Sample Size	Target Power	Actual Power
0.0235	64	0.80	0.801460
0.0235	86	0.90	0.903230
0.0235	105	0.95	0.950129
0.0235	148	0.99	0.990020

The sample size is for each group.

Power Curve for 2-Sample t Test

Figure 2
Power and Sampling Size Graph

PROCESS PERFORMANCE INDEX (PPK)

The Process Performance Index (Ppk) was determined using Process Sigma and Yield for monomers EA/EMA, TFEMA, EGDMA and UV Chr, a Process Capability were analyzed to compare Process Performance Index (Ppk).

For the five monomers (EA/EMA, TFEMA, EGDMA, UV Chr) there are no defects in samples, with the efficiency of 100% and high process sigma confirms that process is capable and meet its predefined requirements.

Table 1

Process Performance Index (Ppk) Indexes for Opal

Component Name	Specification (%)	Average Value (%)	Ppk (Process Sigma and Yield)	Ppk (Process Capability)
EA/EMA	≤ 0.3	0.013	32.83 / Yield:100%	18.27
TFEMA	≤ 0.05	0.002	32.83 / Yield:100%	5.62
EGDMA	≤ 0.1	0.001	32.83 / Yield:100%	32.84
UV Chr	≤ 0.3	0.001	32.83 / Yield:100%	49.52

Data is not normal, the efficiency or yield of 100% and high process sigma confirms that process is capable and in "statistical control"

Table 2

Process Performance Index (Ppk) Indexes for Optiblue

Component Name	Specification (%)	Average Value (%)	Ppk (Process Sigma and Yield)	Ppk (Process Capability)
EA/EMA	≤ 0.3	0.043	32.83 / Yield:100%	2.09
TFEMA	≤ 0.05	0.007	32.83 / Yield:100%	2.12
EGDMA	≤ 0.1	0.001	32.83 / Yield:100%	11.08
UV Chr	≤ 0.3	0.00	32.83 / Yield:100%	30.00

Data is not normal, the efficiency or yield of 100% and high process sigma confirms that process is capable and in "statistical control

Table 1 shows the process Performance Index (Ppk) values of Opal that varies from 5.62 to 49.52 for the Process Capability analysis. Refer to Figure 3 to Figure 6 for Normal Plot.

Table 2 shows the process Performance Index (Ppk) value of Optiblue that varies from 2.09 to 30.00 for the Process Capability analysis. Refer to Figure 7 to Figure 10 for Normal Plot.

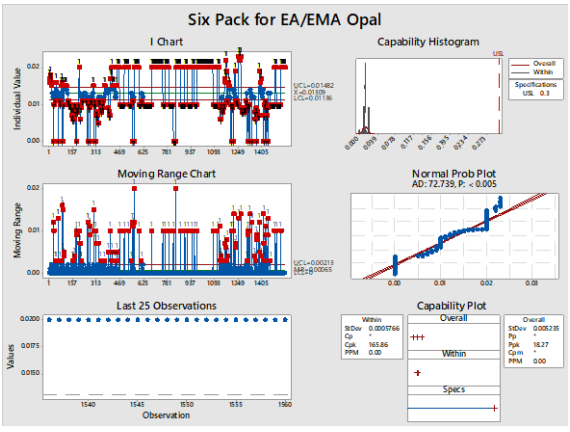


Figure 3

Process Capability Reports for EA/EMA Opal

In Figure 3, it can be seen the Ppk obtained for the monomers EA/EMA was 18.27 and the data results are very lower of the specification (≤ 0.3%) indicating that the data of EA/EMA of Opal buttons are in statical control and meet the requirement of Process capability of ≥ 0.657. Refer to Figure 11 for Ppk calculation.

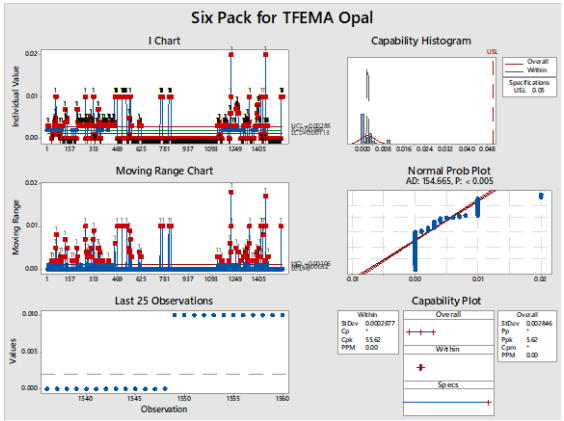


Figure 4

Process Capability Reports for TFEMA Opal

In Figure 4 the Ppk obtained for the monomer TFEMA was 5.62 and the data results are very

lower of the specification (≤ 0.05%) indicating that the data of TFEMA of Opal buttons are in statical control and meet the requirement of Process capability of ≥ 0.657. Refer to Figure 11 for Ppk calculation.

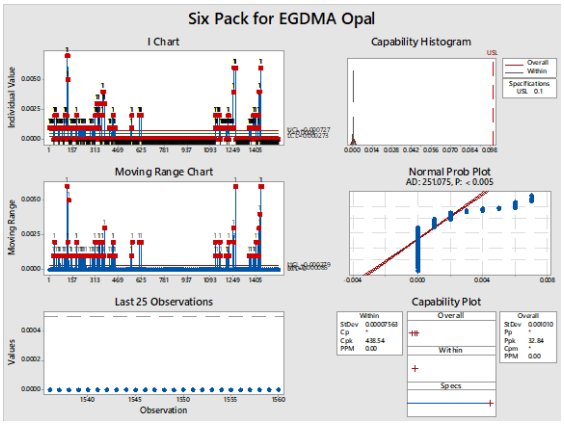


Figure 5

Process Capability Reports for EGDMA Opal

In Figure 5 the Ppk obtained for the monomer EGDMA was 32.84 and the data results are very lower of the specification (≤ 0.1%) indicating that the data of EGDMA of Opal buttons are in statical control and meet the requirement of Process capability of ≥ 0.657. Refer to Figure 11 for Ppk calculation.

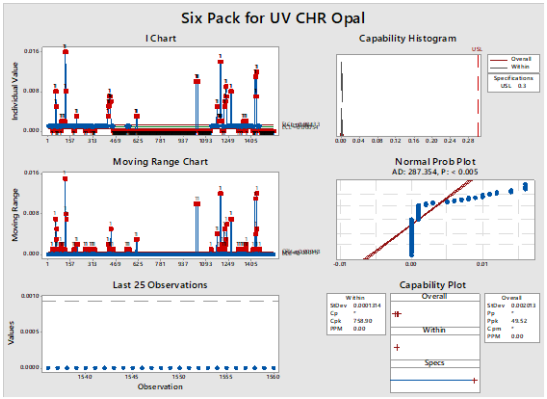


Figure 6

Process Capability Reports for UV Chr Opal

Figure 6 shows the Ppk obtained for the monomer UV Chr was 49.52 and the data results are very lower of the specification (≤ 0.3%) indicating that the data of UV Chr of Opal buttons are in statical control and meet the requirement of Process capability of ≥ 0.657. Refer to Figure 11 for Ppk calculation.

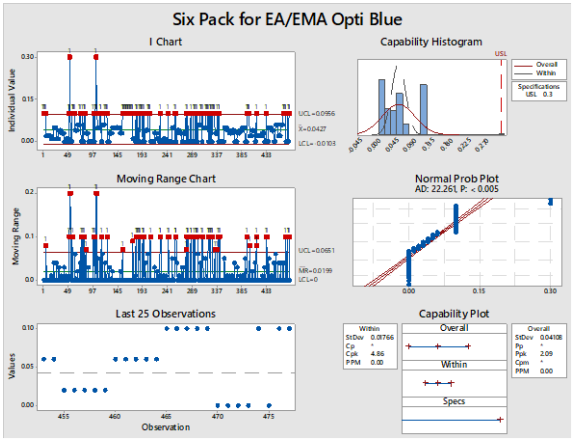


Figure 7

Process Capability Reports for EA/EMA Optiblue

In Figure 7 it can be observed that the Ppk obtained for the monomer EA/EMA of 2.09, most of the data results are lower of the specification (≤ 0.3%). The Ppk in this monomer was not very higher value due to two of the samples falls in the specification limit of 0.3%. Despite this point the Ppk of EA/EMA of Optiblue buttons shows that the data are in statical control and meet the requirement of Process capability of ≥ 0.671. Refer to Figure 12 for Ppk calculation.

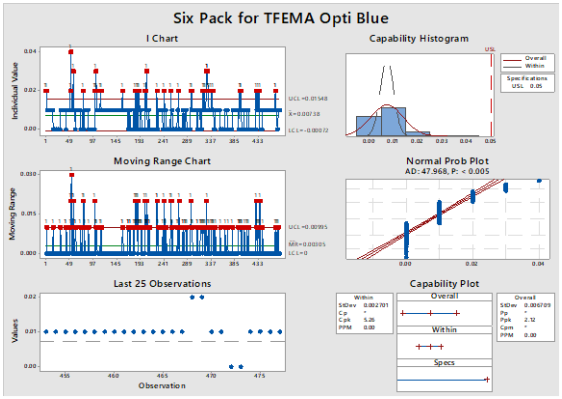


Figure 8

Process Capability Reports for TFEMA Optiblue

In Figure 8 the Ppk obtained for the monomer TFEMA was 2.12, data results are closer of the specification (≤ 0.05%). Ppk of TFEMA of Optiblue buttons shows that the data are in statical control and meet the requirement of Process capability of ≥ 0.671. Refer to Figure 12 for Ppk calculation.

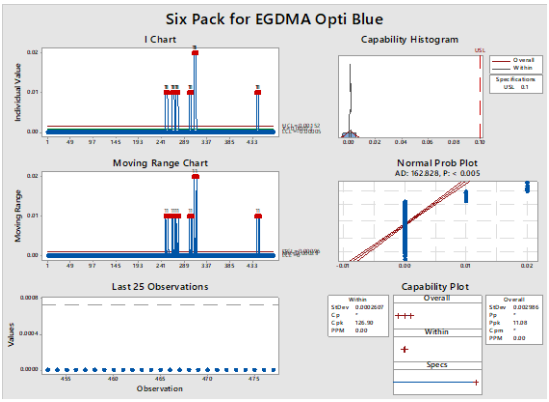


Figure 9
Process Capability Reports EGDMA Optiblue

In Figure 9 the Ppk obtained for the monomer EGDMA was 11.08 and the data results are very lower of the specification (≤ 0.1%) indicating that the data of EGDMA of Optiblue buttons are in statical control and meet the requirement of Process capability of ≥ 0.671. Refer to Figure 12 for Ppk calculation.

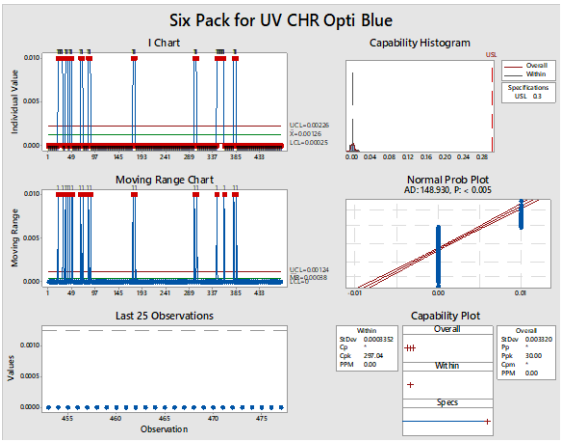


Figure 10
Process Capability Reports UV CHR Optiblue

In Figure 10 it can be observed that the Ppk obtained for the monomer UV Chr was 30.00 and the data results are very lower of the specification (≤ 0.3%) indicating that the data of UV Chr of Optiblue buttons are in statical control and meet the requirement of Process capability of ≥ 0.671. Refer to Figure 12 for Ppk calculation.

According to the "Sensar Sheet Casting and Lens Button Process FMEA Summary Report" the maximum performance Reject Quality Levels (RQL) acceptance criteria of 3.0% is assigned and a 95% Confidence Interval (CI) the minimum required Process Performance Index (Ppk) value is 0.657 for Opal. This value was determined using the Statistical Interval Excel Calculator. Refer to Figure 11.

The maximum sample allow for the calculator is 1000 samples which is more conservative since the samples evaluated from Jun 2018 to May 2020 are 1,560 samples per monomers.

Tolerance Intervals for the Normal Distribution

Input the following information (orange boxes):

Number of samples	1000
Confidence	95.0%
"Coverage" or Proportion in spec	97.0%
Specifications (both, lower, or upper)	upper
Optional – Enter the following three cells if you want a tolerance interval for a particular data set.	
Sample mean	
Sample standard deviation	
# of digits displayed in tolerance interval	

Results		
One-Sided Table Values		
k-value	1.970	To compute the tolerance interval, calculate the mean +/- 1.97 * std dev.
Ppk	0.657	The tolerance interval falls within specs if the Ppk for a sample size = 1000 is greater than or equal to 0.657

Figure 11
Process Performance Index (Ppk) using the Statistical Interval Excel Calculator Opal

For Optiblue the minimum required Process Performance Index (Ppk) value is 0.671. This value was determined using the Statistical Interval Excel Calculator. Refer to Figure 12.

Tolerance Intervals for the Normal Distribution

Input the following information (orange boxes):

Number of samples	477
Confidence	95.0%
"Coverage" or Proportion in spec	97.0%
Specifications (both, lower, or upper)	upper
Optional – Enter the following three cells if you want a tolerance interval for a particular data set.	
Sample mean	
Sample standard deviation	
# of digits displayed in tolerance interval	

Results		
One-Sided Table Values		
k-value	2.012	To compute the tolerance interval, calculate the mean +/- 2.012 * std dev.
Ppk	0.671	The tolerance interval falls within specs if the Ppk for a sample size = 477 is greater than or equal to 0.671

Figure 12
Process Performance Index (Ppk) using the Statistical Interval Excel Calculator for Optiblue

TREND ANALYSIS

Each trend analysis line was evaluated separately based on the data analysis spreadsheets. No negative trend was observed. Refer to Figure 13 to Figure 20.

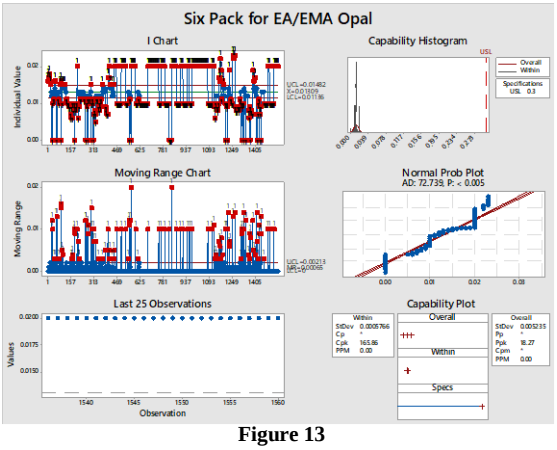


Figure 13
Trend Analysis Plot for EA/EMA of Opal

In Figure 13 no negative trend is observed in the EA/EMA monomers data for Opal Buttons. Variation in the data was observed, but all data analyzed meet specification (≤0.3%) and values falls very low than specification (closer to 0).

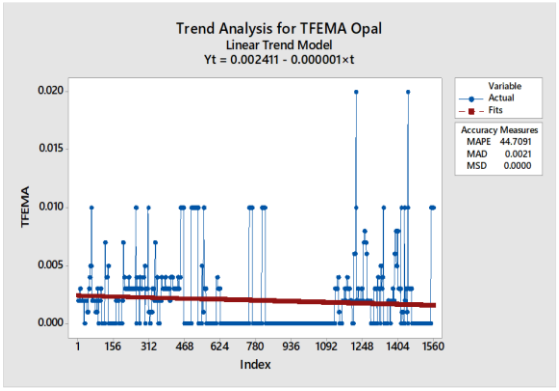


Figure 14
Trend Analysis Plot for TFEMA of Opal

In Figure 14 no negative trend is observed in the TFEMA monomer data for Opal Buttons. Two outliers can be observed in the graph (that are within specification (≤0.05%)), indicating very small variability in the data. Due to all samples results are within specification and the trend is not negative, we can conclude that the annealing process is in control.

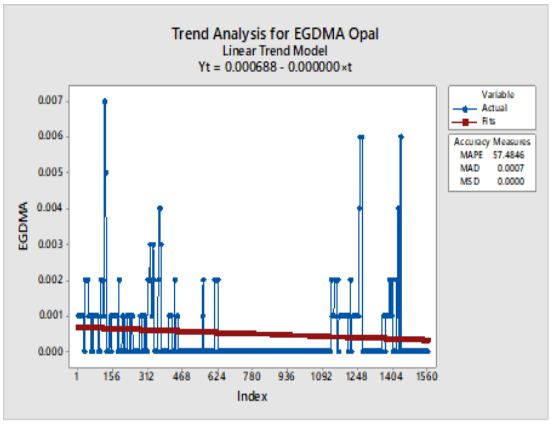


Figure 15
Trend Analysis Plot for EGDMA of Opal

In Figure 15 no negative trend is observed in the EGDMA monomer data for Opal Buttons. Some outliers can be observed in the graph (that are within specification (≤0.1%)) due to small scale. Most of the data values fall to 0, indicating that the annealing process is in control.

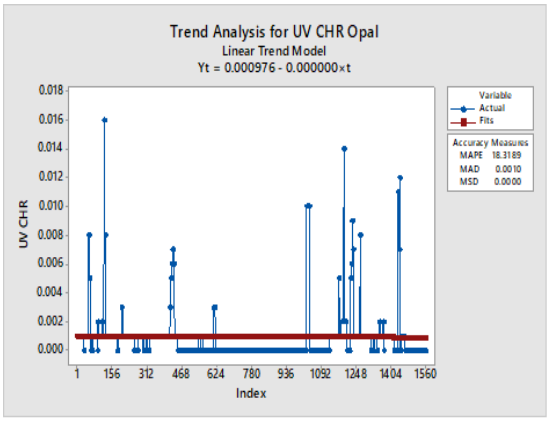


Figure 16
Trend Analysis Plot for UV CHR of Opal

In Figure 16 no negative trend is observed in the UV Chr monomer data for Opal Buttons. Most of the values fall to 0, indicating that the annealing process is in control, where the UV Chr is no detected in most of samples.

In Figure 17 no negative trend is observed in the EA/EMA monomers data for Optiblue Buttons.

Two (2) outliers are observed, these values fall in the specification (≤0.3%). This trending graph indicate that the annealing process is in control.

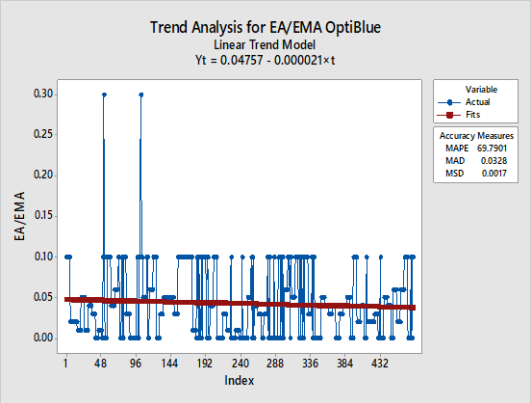


Figure 17
Trend Analysis Plot for EA/EMA of Optiblue

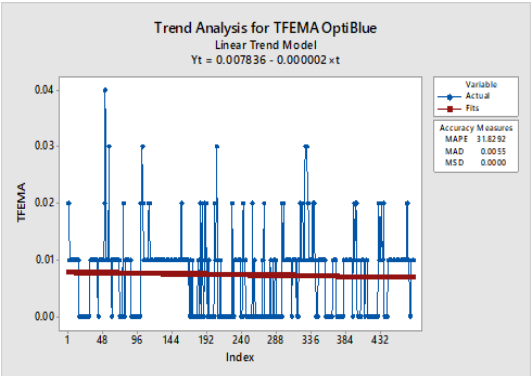


Figure 18
Trend Analysis Plot for TFEMA of Optiblue

In Figure 18 no negative trend is observed in the TFEMA monomer data for Optiblue Buttons. This trending graph indicate that the annealing process is in control. One (1) outlier is observed, that is within specification (≤0.05%).

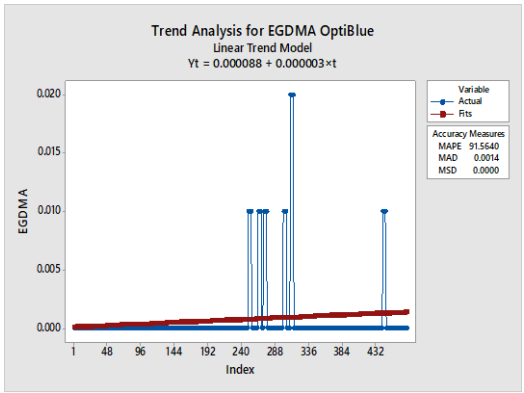


Figure 19
Trend Analysis Plot for EGDMA of Optiblue

In Figure 19 no negative trend is observed in the EGDMA monomer data for Optiblue Buttons. This trending graph indicate that the annealing process is in control, where most of the samples do not detected residuals of EGDMA. Two (2) outliers are shown but they represent a very low value comparing with monomer specification (≤0.1%).

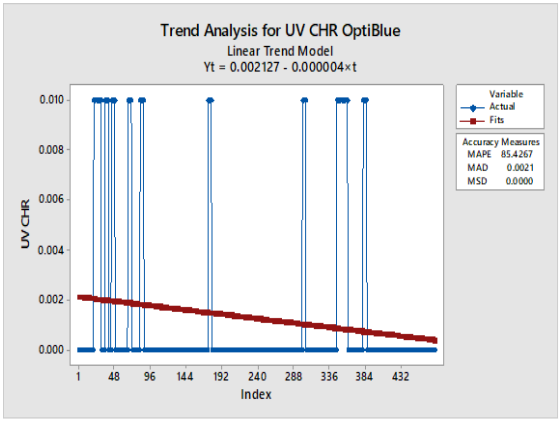


Figure 20
Trend Analysis Plot for UV CHR of Optiblue

In Figure 20 no negative trend is observed in the UV Chr monomer data for Optiblue Buttons. This trending graph indicate that the annealing process is in control, where most of the samples do not detect residuals of UV Chr and values are very lower than specification (≤ 0.3%).

CONCLUSION

The residual monomer levels testing measures the amount of monomer and crosslinker not polymerized or removed by annealing process. The annealing process is a validated process and equipment used are qualified and monitored using JJSV calibration system.

Process Performance Index (Ppk) value varies from 5.62 to 49.52 for the Opal and 2.09 to 30.00 for Optiblue, which confirm annealing process is a capable and is in statistically control. According to Statistical Sampling for Validations procedure, with a Severity Level of (3) from the "Sensar Sheet Casting and Lens Button Process FMEA Summary Report", the maximum performance Reject Quality Levels (RQL) acceptance criteria of 3.0% is assigned and a 95% Confidence Interval (CI) the

minimum required Process Performance Index (Ppk) value for opal is 0.657, for Optiblue the minimum Ppk is 0.671 [4].

No negative trend was observed in any of the components. No OOS, ERs or NRs were generated during the time frame evaluated (from June 2018 to May 2020 for Opal and January 2019 to May 2020 for Optiblue) [4].

Following review of applicable process step and hazard risk assessment using "Sensar Sheet Casting and Lens Button Process FMEA Summary Report", there is no impact foreseen in the test elimination. Even if testing will be eliminated, every Production Order in annealing oven run will be analyzed and if material is not completely polymerized it will fail other identification test in the downstream testing (Haze, FTIR, RI or UV/VIS). There is no change to the form fit or function of the material / product, and no changes to material composition or further inspections, based on that there is no new severity or changes in the risk to update the test method.

Based on this assessment findings and retrospective data collected, it is recommended to:

Eliminate the Post Annealing Monomer Residual Test for EA/EMA, TFEMA, EGDMA, UV Chromophore. This evaluation confirm that the annealing process is a capable and is in statistically control. The annealing process is a validated process and equipment used are qualified and monitored using JJSV calibration system. Every annealing oven run will be analyzed and if material is not completely polymerized it will fail other downstream identification test (Haze, FTIR, RI and UV/VIS). With Post Annealing Monomer Residual Test elimination, it can reduce the release time for each production order and reduce exponentially HPLC's and UHPLC equipment spare parts and maintenance cost and waste.

REFERENCES

[1] Boyd, K. (2021). *IOL Implants: Lens Replacement After Cataract.* [American Academy of Ophthalmology]. [Online] Available: https://www.aao.org/eye-health/diseases/cataracts-iol-implants.

[2] DeFeo J. A. (2020). *DMAIC Process & Methodology: An Essential Guide.* [Juran]. [Online] Available: https://www.juran.com/blog/dmaic-attaining-superior-quality-sustainable-results/

[3] Pena, M. "Monomers residuals data summary and evaluation for OptiBlue Soft Acrylic Buttons". Revision 02. JJSV, Anasco, Puerto Rico, 2020.

[4] Vargas, B. "Monomers residuals data summary and evaluation for Sensar and Sensar UV^2 Soft Acrylic Buttons". Revision 01. JJSV, Anasco, Puerto Rico, 2020.