SiO2 MATERIALS SCIENCE℠

Vial Coating Stability Filled with Water for Injection (WFI)

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EXECUTIVE SUMMARY

SiO2 Materials Science, Inc. (SiO2) 6 mL vials were filled with WFI and stored for various periods of time at different temperatures and tested for various characteristics that would indicate coating stability and suitability for use. Orthogonal testing indicated that the barrier coating system stayed intact and resisted the chemical challenge posed by the water for injection (WFI).

INTRODUCTION

SiO2's containers for parenteral medications stand out from all other polymer and glass containers for parenteral solutions on the market today for the following reasons:

1. The polymer material, cyclic olefin polymer (COP), has excellent toughness and impact resistance to breakage.
2. The inner surface of the polymer container is coated using plasma enhanced chemical vapor deposition (PECVD) with a 3-layer barrier coating system that provides pH resistance, oxygen barrier properties, and leachable resistance. Furthermore, the barrier coating system in contact with the drug product is alkali metal and polydimethylsiloxane (PDMS/silicone oil) free.
3. Injection stretch blow molding processing produces primary containers with high dimensional consistency not attainable by borosilicate glass forming.
4. The SiO2 container incorporates a unique unit dose identification. Traceability can be shown down at the unit level.

PURPOSE

To evaluate the stability of vials filled with WFI in order to understand the behavior of both the cyclic olefin polymer matrix and the PECVD barrier coating when exposed to WFI for long periods of time and at accelerated conditions.

BACKGROUND

WFI is one of the most difficult to package solvents due to its corrosive effects on glass packaging components. WFI was used as a model drug solvent vehicle to help gain an understanding of the robustness of the coating over time and accelerated conditions.

METHOD

The study matrix below looks at temperature, relative humidity and storage time conditions to accelerate any potential impact on stability to the coating quality of the vial. The vials were 6 mL COP coated on the inside with the same barrier coating system.

Temperature/ %Relative Humidity	Time (months) in Storage
30°C/65%RH	0
30°C/65%RH	3
30°C/65%RH	6
30°C/65%RH	9
30°C/65%RH	12
40°C/75%RH	3
40°C/75%RH	6
40°C/75%RH	9

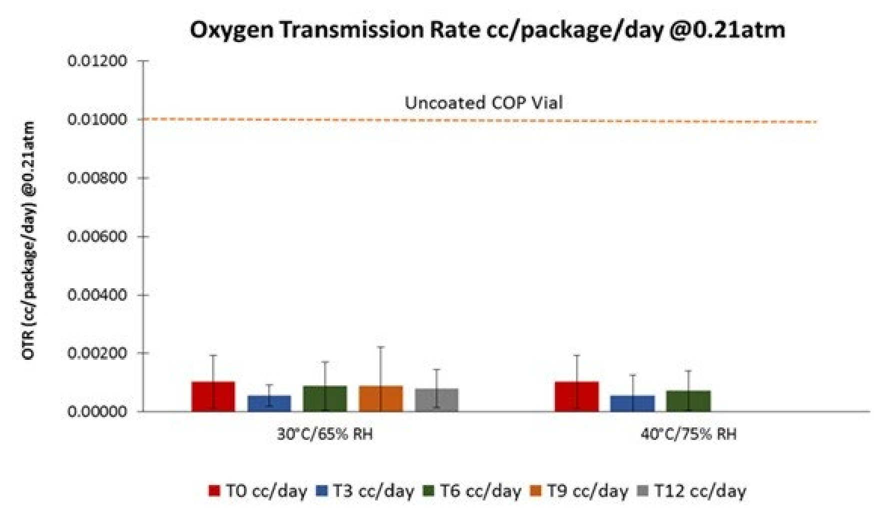
Barrier system coated 6 mL vials produced from a single lot were filled under laboratory conditions with water for injection (WFI), steam sterilized for 30 min at 123°C maximum temperature, and challenged under two conditions, 30°C and 65% Relative Humidity (RH) and 40°C and 75% RH. Transit time from the filling site to SiO2 facility was approximately 8 weeks, therefore SiO2 Time 0 samples had experienced 2 months storage time.

Vials were pulled for testing after five timepoints (T0, T3, T6, T9, and T12) over the course of 12 months for 30°C and 65% RH and three time points over 6 months (T0, T3, and T6) for 40°C and 75% RH 30. These tests included Oxygen Transmission Rate, Rate of Silicon Dissolution, Chemical Integrity Test (CI-9), Particle Count (i.e., Light Obscuration and Membrane Microscopy), and Coating Thickness.

RESULTS

OXYGEN TRANSMISSION RATE (OTR)

Vials were emptied and analyzed via the Mocon OpTech O2 Platinum which is an optical measurement method. An O_2 sensor was placed inside each article and sealed with a glass slide that was epoxied over the vial opening under a reduced oxygen environment (i.e., nitrogen filled glove box). The internal O_2 partial pressure was measured daily for 7-9 days until the system reached equilibrium. The linear regression of O_2 measurements was determined and the resulting slope was converted to oxygen transmission rate (OTR) in units of cubic centimeters (cc) per package per day at 0.21 atmospheres.



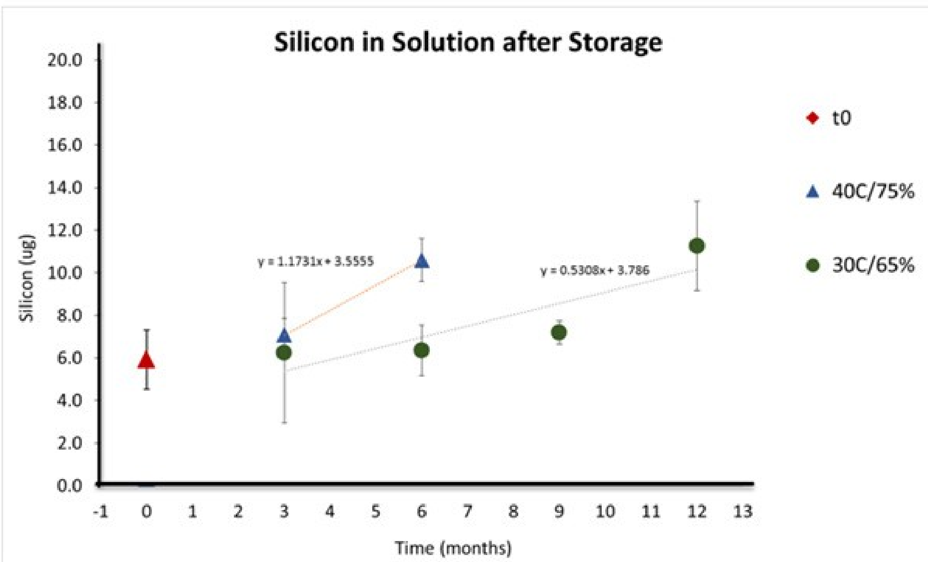
TEST CONCLUSIONS

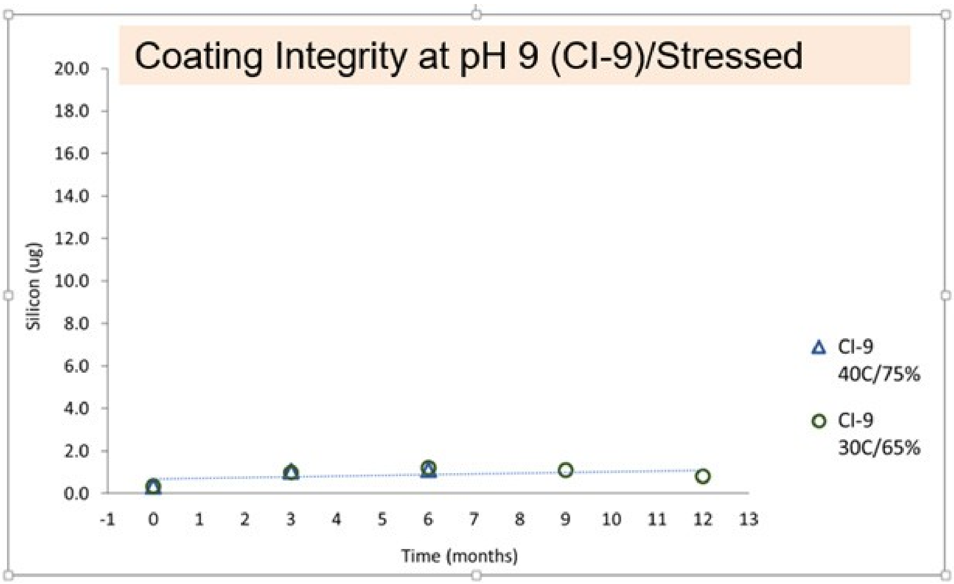
Low and consistent OTR measurements indicate a stable and coherent barrier system that does not change over time irrespective of challenge condition. It is important to note here that our target mean OTR is 0.001 cc/package/day.

DISSOLVED SILICON & COATING INTEGRITY AT pH9

EXPERIMENTAL

After storage, the WFI was measured neat for total dissolved silicon via Inductively Coupled Plasma-Optical Emission Spectroscopy (ICP-OES). 20 samples were measured per condition. After this testing all vials were emptied and allowed to sit under the laminar flow hood until visually dry. Empty vials were filled with 7mL of Potassium Phosphate, pH9 and stored at 40°C for 72 hrs per Laboratory Method CI-09. Solution was then measured for Si via ICP-OES.





CONCLUSIONS

Low values for dissolved silicon in both testing modes indicates a stable barrier coating system with minimal change in thickness. As was expected, the dissolution rate was higher with elevated temperature.

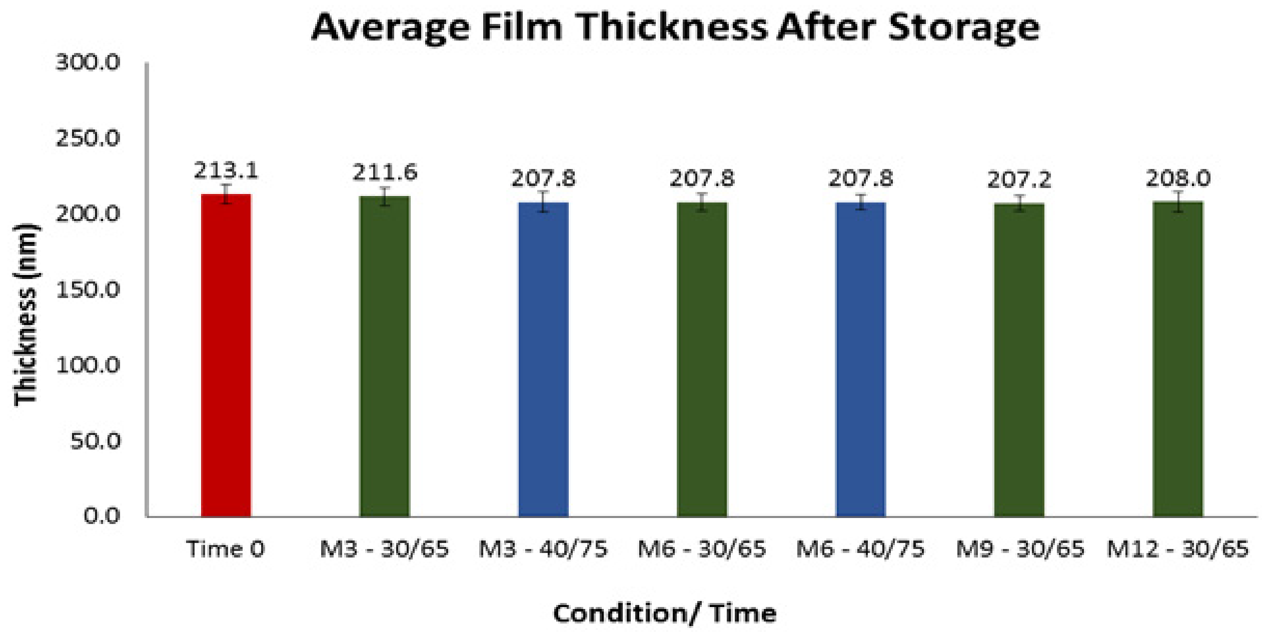
CI-9 was performed as a “shock” test to determine the bonding integrity of barrier coating system after challenge conditions. (CI-9) Si in solution values of 1.1ug or less indicate stable coating. If the barrier coating system was delaminating the dissolved silicon would be expected to be between 10 and 100 µg. If the protective layer was missing altogether, the dissolved silicone would be expected to be above 100 µg.

FILM THICKNESS VIA SPECTRAL REFLECTANCE ANALYSIS

Spectral reflectance measures the amount of light reflected from a thin film over a range of wavelengths, with the incident light normal (perpendicular) to the sample surface. SiO2 utilizes this technique as a process check to determine that the specified thickness of the various coatings that make up the barrier coating system are applied. In this study the technique was used to determine if any degradation of the film occurred during storage.

EXPERIMENTAL

The Filmetrics F50 Thin Film mapper was utilized for thickness analysis. The instrument has a minimum detection limit of a film thickness of 50 nm. 20 samples were measured at each time point with 56 optical measurements taken per sample. The measurements were made around the circumference of the vials on the flat surfaces indicated below in the picture. Data is reported as the mean thickness in nanometers (nm). These were the same vials used for Si in Solution: After storage, solution was decanted and measured for Si in solution, then dried and measured for thickness.



CONCLUSION

No significant change in thickness of the barrier coating system was observed for either storage condition. These results suggests that the coating is resistant to degradation by WFI at these storage conditions.

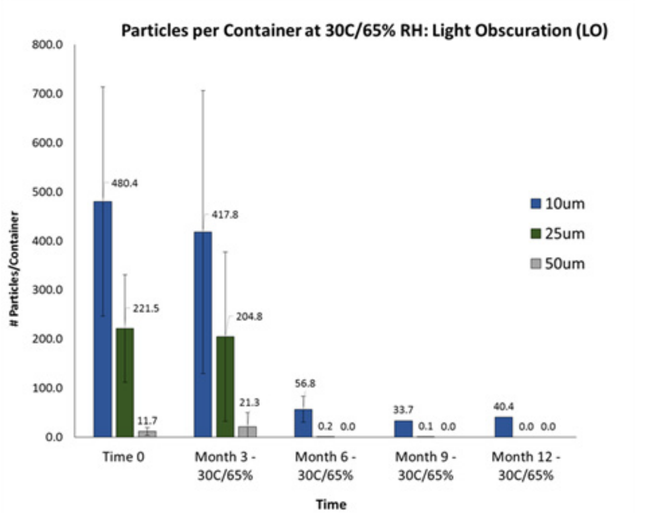
PARTICLES BY LIGHT OBSCURATION (LO)

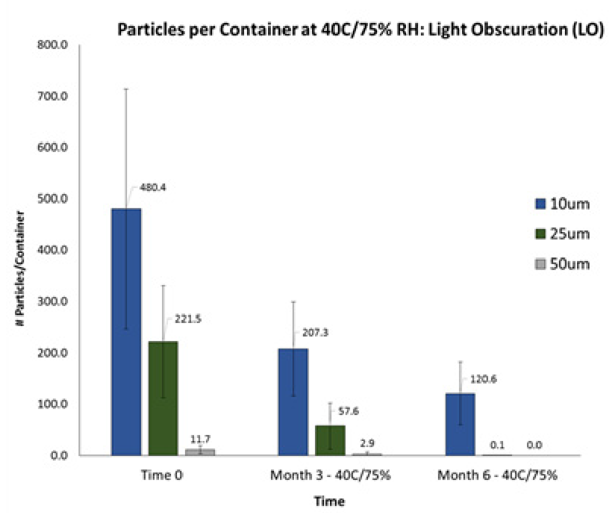
WFI stored in the vials was analyzed by light obscuration to understand if particles of the barrier coating system sloughed from the walls with storage time. Particle counting is performed by passing a fluid with suspended particles between a light source and a light detector. Particles of sufficient size block the light to the detector over a period of time corresponding to the size of the particle.

EXPERIMENTAL

- Beckman Coulter HIAC 9703 and Beckman Coulter HIAC 3000A Liquid Particle
- 30 samples tested per time point yielding 30 separate data points
- Reported as average number of particles per container

The following graphs show the particles found in the solutions over time at the two temperature and humidity conditions.





CONCLUSIONS

- T-0 and T-3 month were analyzed on different instruments than subsequent data points. The initial testing being performed in a pilot facility. The latter testing was performed in the production facility. Dilution of pooled volume may have been a source of secondary contamination. The cleanliness of the manufacturing environment may of also of been a contributor to the lower particle counts.
- All counts were below the USP <788> "Particulate Matter in Injections" specification of 6000 units of particles/container (10um) and 600 units of particles/container (25um).
- The data show no increase in particles over time – the barrier coating system maintains integrity during the aging study.

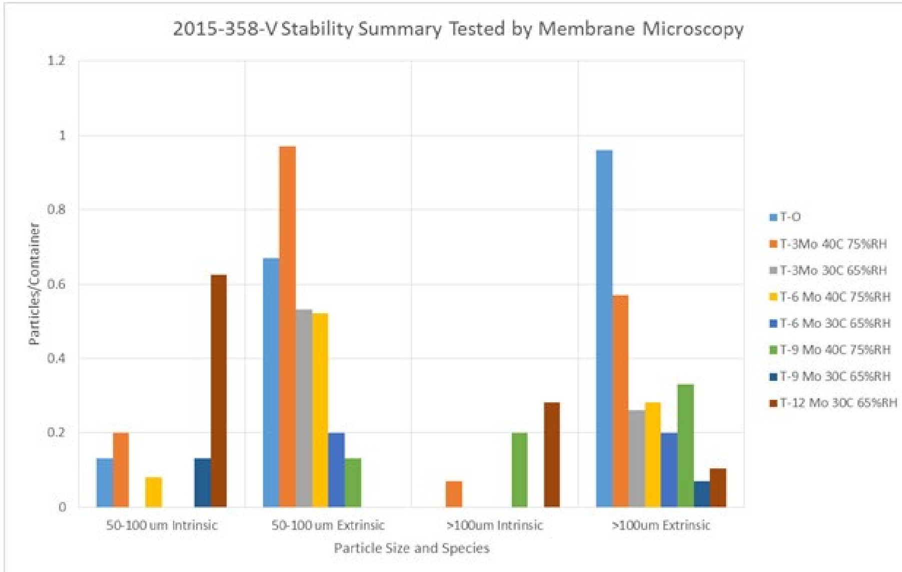
PARTICULATES BY MEMBRANE MICROSCOPY (MM)

The WFI from the containers was also analyzed by Membrane Microscopy to understand if particles of the coating sloughed from the walls with exposure to WFI. Membrane Microscopy is a technique whereby particles in solution are passed through a membrane filter and trapped on the surface. The filter is then dried and observed (usually under microscopic magnification) and then the particles are sized and counted. This technique is advantageous in that the particles can be observed optically for indication of origin.

EXPERIMENTAL

- Membrane filtration: Millipore 0.45um HARP black nitrocellulose filters, 100X magnification, BX53 compound microscope.
- Extraction 20 inversions, seals removed, rinsed, stoppers removed and dispensed directly on membrane.

The following graph show the particles found in the solutions over time at the two temperature and humidity conditions



CONCLUSIONS

- In comparison to each other there are far more extrinsic particles versus intrinsic particles present in the solution as observed under the microscope. Extrinsic particles are debris from other than the barrier coating process and material. They may include filling environment/process artifacts as well as elastomeric closure debris, residue and filler bloom. Intrinsic particles are identified as glassy plates that are easily distinguishable from other particulate matter and are related to the barrier coating degradation.
- Extrinsic particle contaminants (described above) are present at all time points and storage conditions. They did not increase over time. This may be due to handling and cleanliness in the laboratory where the vials were filled or the preparation of the elastomeric closures used on the vials.
- Intrinsic particles remain low in number and do not increase over time. This evidence is indicative of the fact that the coating did not change, degrade or otherwise delaminate over time in contact with WFI.
- Overall, the data show no increase in particles over time – the barrier coating system maintains integrity during the aging study.

OVERALL CONCLUSION

- The vials and barrier coating system remained intact and functional after testing using orthogonal analytical methods.
- Specifically, the oxygen transmission rate, film uniformity, and high pH shock test indicated that the barrier coating was functional, intact, and without flaw. Particle data indicated higher than expected results at times. This is the one test whose results are incumbent upon many factors other than the barrier coating itself; including elastomeric seal (over- processing, handling, and washing efficacy can affect particle burden), processing of the fill fluid, and the ambient filling environment.