SiO2 Medical Products™
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SiO_2 Vial with Trilayer Oxygen Barrier Coating; Stability in the presence of Water for Injection (WFI)

Technical Report Series 2016-005

Keywords: WFI, stability, vial, trilayer, oxygen, transmission rate, filmetrics, coating, dissolution, particles

Executive Summary

SiO_2 Medical Products, Inc. (SMP) 6 mL vials were filled with WFI and stored for various periods of time and temperature and tested for various characteristics that would indicate stability and suitability for use. Orthogonal testing indicated that the trilayer oxygen barrier coating resisted the challenge posed by the WFI.

Introduction

SMP's containers for parenteral medications stand out from all other polymer and glass containers for parenteral solutions on the market today for many reasons.

1. The polymer material of construction lends itself to break resistance and robustness.
2. The inner surface of the polymer container is coated using plasma enhanced chemical vapor deposition (PECVD) with three layers of silicon based material that provides pH resistance, oxygen barrier properties, and leachable resistance. In addition, due to the materials of construction, the container surface is metal and polydimethylsiloxane (PDMS/silicone oil) free.
3. Injection stretch blow molding processing produces primary containers wth high dimensional consistency not attainable by borosilicate glass forming.
4. The SMP container incorporates a unique unit dose identification. Traceability can be shown down to 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

This study looks at two conditions that test the upper limits of storage conditions to accelerate any potential impact on stability to the coating quality of the vial.

Component	Sterilization Parameters	Temperature/ %Relative Humidity	Time (months) in Storage
6mL COP Vial w/ Trilayer Coating	30' @ 123°C	30°C/65%RH	0
6mL COP Vial w/ Trilayer Coating	30' @ 123°C	30°C/65%RH	3
6mL COP Vial w/ Trilayer Coating	30' @ 123°C	30°C/65%RH	6
6mL COP Vial w/ Trilayer Coating	30' @ 123°C	30°C/65%RH	9
6mL COP Vial w/ Trilayer Coating	30' @ 123°C	30°C/65%RH	12
6mL COP Vial w/ Trilayer Coating	30' @ 123°C	40°C/75%RH	3
6mL COP Vial w/ Trilayer Coating	30' @ 123°C	40°C/75%RH	6
6mL COP Vial w/ Trilayer Coating	30' @ 123°C	40°C/75%RH	9

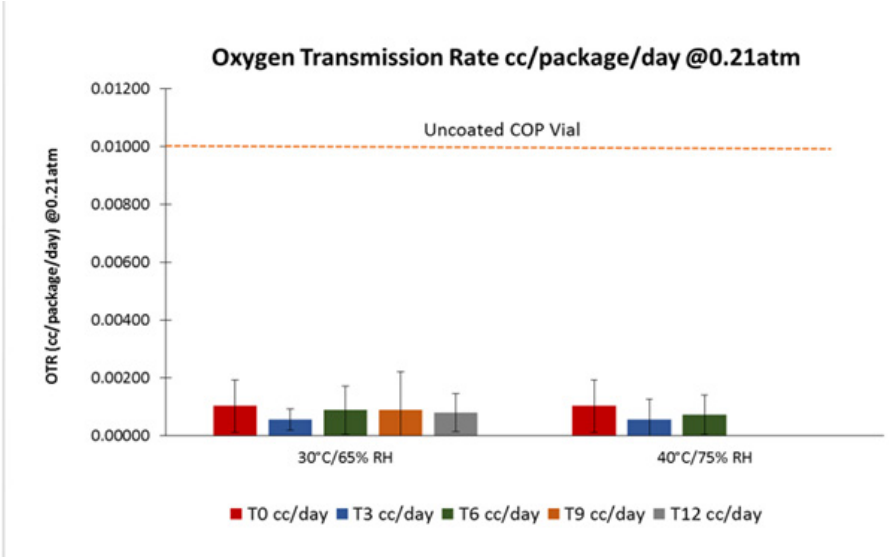
6 mL vials produced from a single lot were filled under laboratory conditions with water for injection (WFI), steam sterilized for 30 min at 123°C maximum temperature, and challenged under two conditions, 30°C and 65% Relative Humidity (RH) and 40°C and 75% RH. Transit time from the filling site to SMP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

At five time points (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 samples were pulled and tested according to an internal testing panel at SMP. These tests included Oxygen Transmission Rate, Rate of Silicon Dissolution, Chemical Challenge Test (CI-9), Particle Count (Light Obscuration and Membrane Microscopy), and Coating Thickness.

Results

OXYGEN TRANSMISSION RATE (OTR)

Vials were emptied and analyzed via the Mocon OpTech O_2 Platinum which is an optical measurement method. An O_2 sensor was placed inside each article and sealed with a glass slide that is epoxied over the vial opening under a reduced O_2 environment (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 transmission rate.



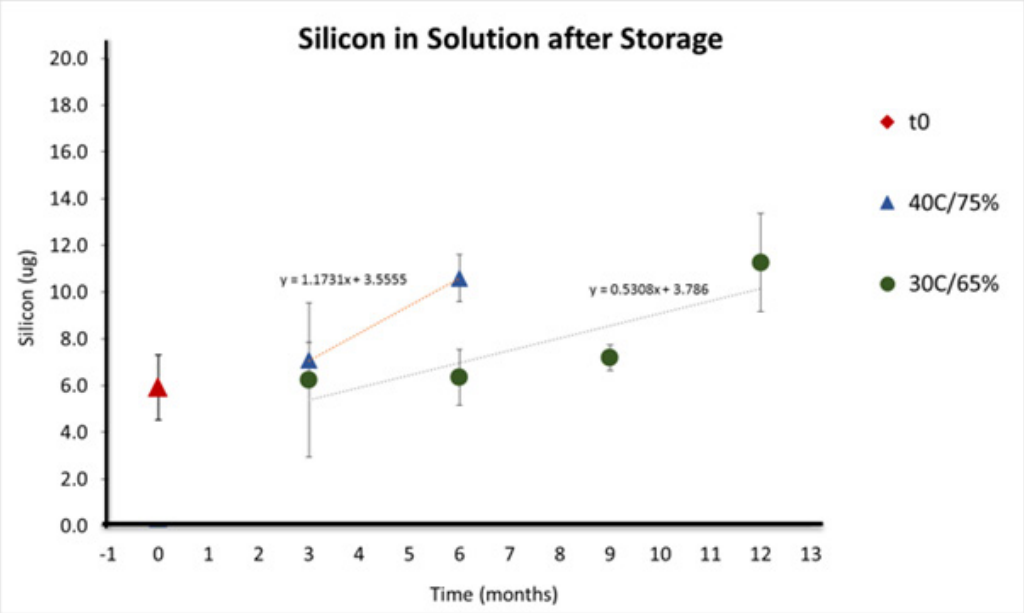
Test Conclusions

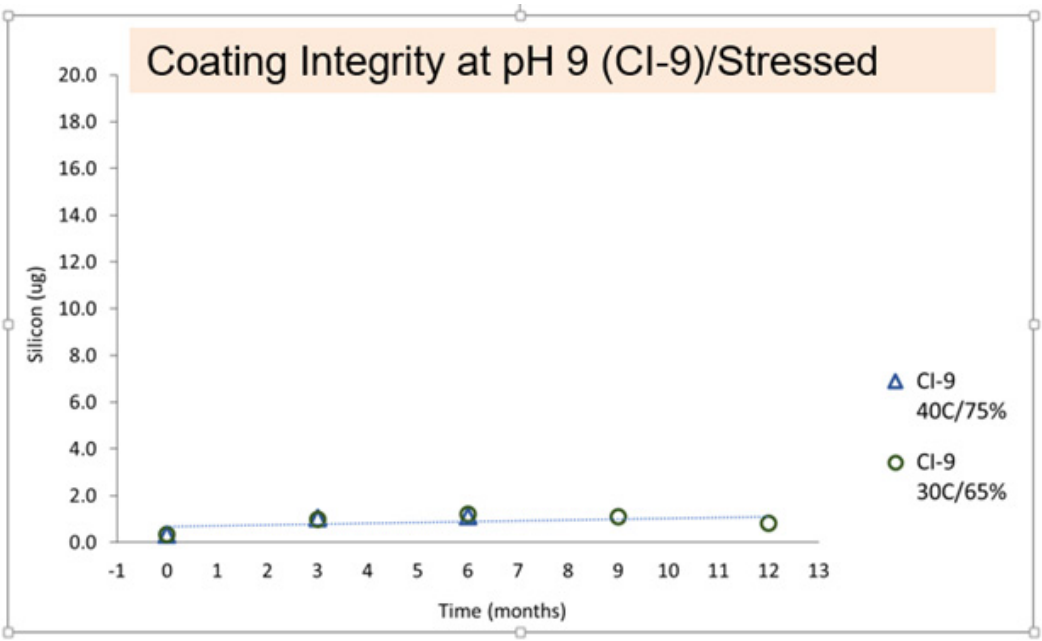
Low and consistent OTR measurements indicate a stable and coherent barrier system that does not change over time irrespective of challenge condition. It is important to note here that our target mean OTR is 0.001 pkg/cc/day.

Dissolved Silicon & Coating Integrity at pH 9 (CI-9)

Experimental

After storage, the WFI was measured neat for total Si via Inductively Coupled Plasma-Optical Emission Spectroscopy (ICP-OES). 20 samples were measured per condition. After this testing all containers 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 indicate stable coating system and correlates to minimal change in thickness. If, hypothetically, the barrier layer was damaged or removed by the WFI during storage one would expect to see upwards of 300 to 400 µg of Si in solution as this is the total mass of the barrier layer. This conclusion is corroborated by film thickness measurements which indicate no change in the total thickness of the coating.

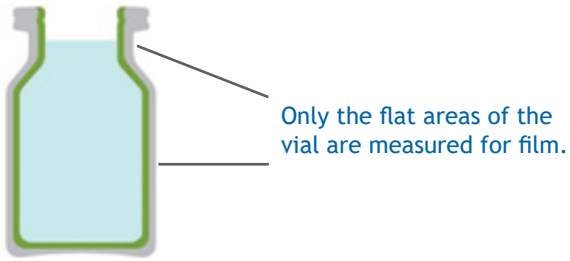
As was expected, the dissolution rate was higher with elevated temperature. CI-9 was performed as a "shock" test to determine integrity of coating stack after challenge conditions. (CI-9) Si in solution values of 1.1ug or less indicate stable coating. Previously generated data for Type 1 glass vials tested using CI-9 was 27 µg or about 9 times that of the Trilayer vials. Total amount of silicon in barrier system is approximately 300 – 400 µg in the 6 mL vial.

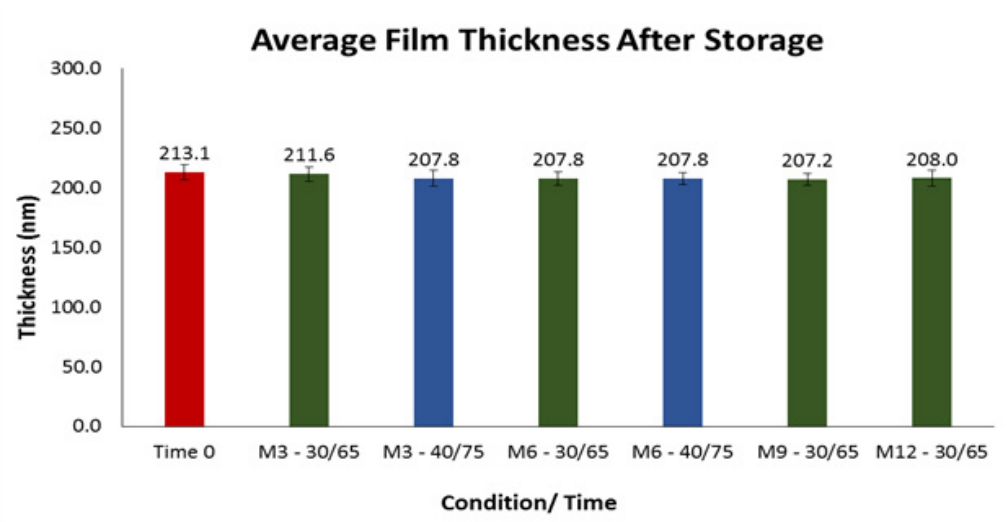
Film Thickness via Spectral Reflectance Analysis

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. SMP utilizes this technique as a process check to determine that the specified thickness of the various coatings that make up the trilayer 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 this 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 are made around the circumference of the container on the flat surfaces indicated. Data is reported as the mean thickness in nanometers (nm). These were the same samples used for Si in Solution: After storage, solution was decanted and measured for Si in solution, then dried and measured for thickness.





Conclusion

No degradation of the container coating thickness was observed for either condition.

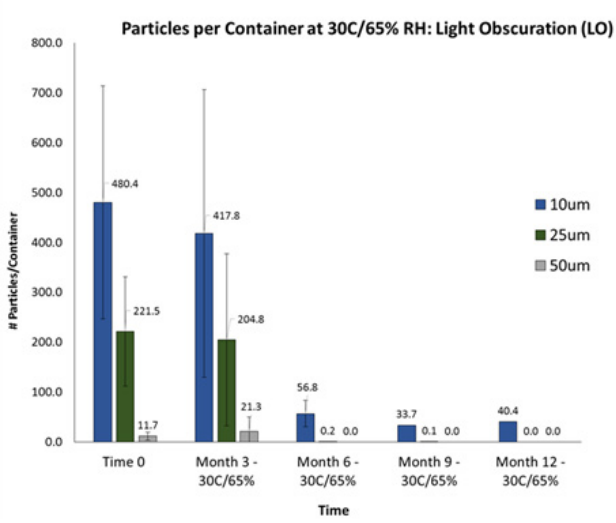
Particles by Light Obscuration (LO)

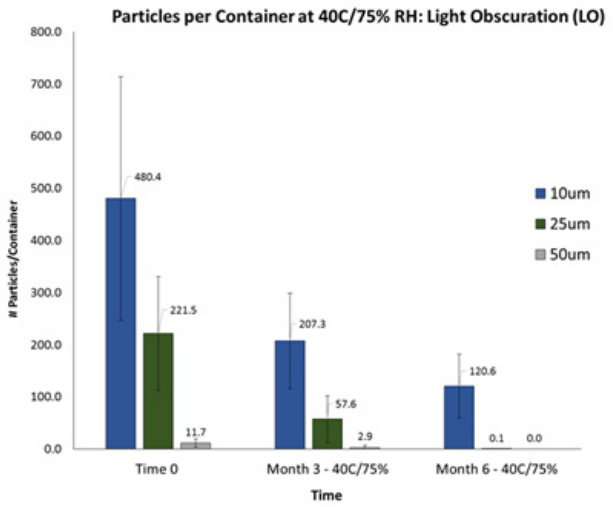
The WFI from the containers was analyzed by light obscuration to understand if particles of the coating sloughed from the walls with exposure to WFI. Light obscuration particle counting is an analytical technique whereby an aliquot of the sample is sipped into a tube and pumped between a light source and a light detector. Particles of sufficient size block the light and this time period is measured and converted into a particle size; physics dictating that the bigger the particle, the longer the light will not be detected. This time interval corresponds to an ideal particle dimension which is the output of the instrument.

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.
- 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 trilayer coating maintains integrity during the aging study.

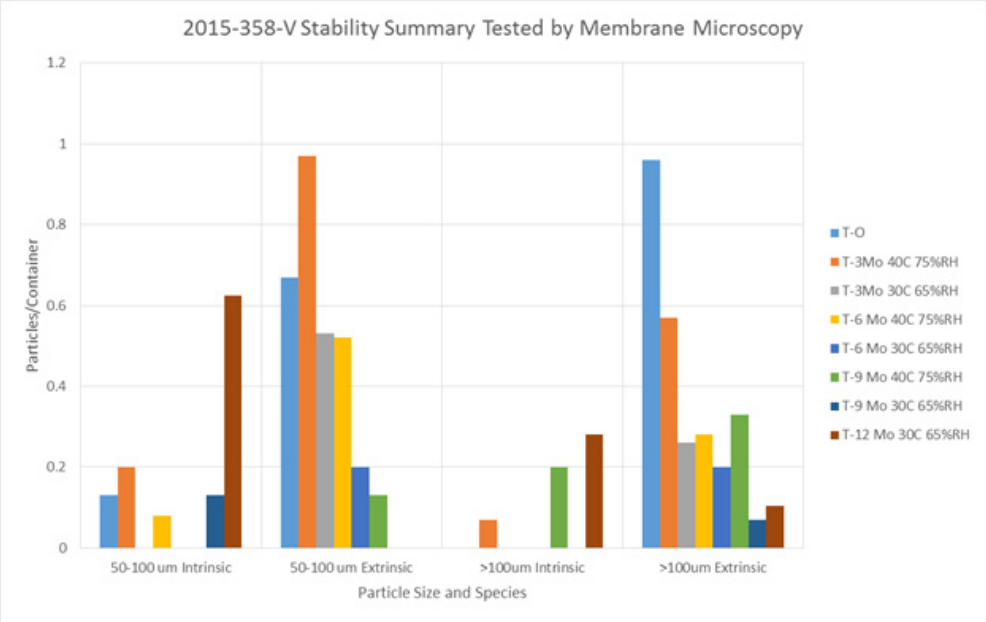
Particulates by Membrane Microscopy (MM)

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 trilayer coating maintains integrity during the aging study.

Overall Conclusion

- The vials and trilayer coating 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, coherent, 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.