

Hybrid Pharmaceutical Vials for Lyophilized Biological Drugs and Vaccines

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Liquid Formulation Stability and Compatibility in Glass – A Formidable Challenge

Most parenteral therapeutic drugs are formulated liquids that are ready to be injected or infused directly into a patient's tissue. Typical formulations contain the active pharmaceutical drug substance, water and a host of other inactive ingredients called excipients that stabilize and preserve the drug's therapeutic benefits. Biologic drug substance complexity has steadily increased over the years, which are more challenging to preserve and stabilize in liquid formulations. Refrigeration or even frozen storage may not be a viable nor practical option. If the drug stability in a liquid formulation cannot achieve basic regulatory storage requirements, then freeze drying (i.e., lyophilization) may be the next best option. Many vaccines are freeze-dried for improved shelf stability, particularly when refrigeration is unavailable as in third world countries. Freeze drying turns a liquid drug or vaccine formulation into a dry solid material that is far more stable at room temperature and simplifies transport. Many companies that have launched COVID-19 vaccines into the marketplace are actively exploring lyophilization to circumvent the burdens of sub-zero cold chain storage.¹⁻³

Irrespective of liquid or lyophilized formulations, primary containers for storage and injection of parenteral drugs are made of borosilicate glass with few exceptions. Specifically, Type I borosilicate glass has been a mainstay of the pharmaceutical packaging industry for over 100 years.⁴ Compared to other traditional glass compositions, borosilicate has the best balance of chemical inertness, hydrolytic stability, and thermal shock resistance to breakage.⁵ However, the evolving biologic drug pipeline has resulted in formulations with extremes of pH, ionic strength, surfactant concentration, viscosity, and drug concentration.

Some formulations have challenged the limits of borosilicate glass resulting in both chemical and physical incompatibilities that are not easily managed. For example, more acidic liquid formulations can accelerate ion exchange with the glass⁶ Metal ions leaching from glass into the formulation can result in undesirable chelation reactions with the drug molecule or excipients and trigger glass delamination. Some proteins in liquid formulations can adsorb and denature on glass, which can result in undesirable aggregates in the drug formulation.⁷

Some freeze-dried formulations can impose enough physical strain to fracture and shatter glass vials.^{8,9} This is exacerbated at higher fill volumes and with formulations containing cryoprotectants such as mannitol. Fill volumes rarely exceed about 40% of the nominal vial volume to minimize the chance of this type of failure. The wettable surface characteristics of glass can promote wicking of the formulation up the side wall and result in fogging upon freeze-drying.¹⁰ This can complicate inspection or compromise quality.

Hybrid Primary Packaging Developed for Liquid Biologic Formulations

The use of SiO₂ hybrid pharmaceutical vials for lyophilized biologic drugs and vaccines offer important advantages compared to borosilicate glass vials. These advantages include: (1)

improved heat transfer and batch consistency, resulting in more consistent drying across a batch, (2) ending glass breakage at higher fill volumes and (3) eliminating wall residue.

SiO₂ Materials Science (SiO₂) developed primary packaging targeted at liquid biologic formulations. The materials of construction were designed to overcome the many shortcomings of borosilicate glass. Materials science and engineering principles and creative problem solving were applied over 10 years of research and development to provide an innovative solution to the many problems with borosilicate glass. The result was a proprietary hybrid material that blended the best properties of plastic and glass into a unique primary container packaging system.

The predominant problems with borosilicate glass that are either eliminated or significantly improved with SiO₂ primary packaging include breakage,⁴ delaminated glass particles,^{4,6,7} metal ion leachates,^{4,11} variable drug contact surfaces,¹¹ dimensional variation,¹² and hydrolytic instability.^{4,13} A rigorous battery of compatibility testing¹⁴⁻¹⁹ was conducted to showcase the robust physical, chemical, and thermal stability of SiO₂ hybrid primary containers to a wide range of liquid formulations. Testing was supplemented by comprehensive compliance testing, which is included in the drug master file submission with the FDA.

Two commercial SiO₂ hybrid packaging products are currently on the market.^{20,21} Many more SiO₂ products are at various stages of drug stability and clinical evaluation with wide a range of pharmaceutical biologic formulations. The success and benefits of SiO₂ hybrid syringe and vial products for liquid formulations was published or disclosed elsewhere,¹⁴⁻²¹ but not the focus of this publication. However, many of the same advantages for liquid formulations also benefit freeze-dried formulations.

SiO₂ hybrid vials are manufactured with exterior and neck finish dimensions that conform to ISO 8362-4:2011 standards. This ensures identical exterior nominal dimensions and finish to ISO 10R borosilicate glass vials. However, due to a slightly thicker bottom and wall, the interior dimensions of the SiO₂ hybrid vials do not exactly match the ISO standards. As a result, the nominal fill volume of the SiO₂ hybrid vials is 10 mL and the overfill volume is about 11.5 mL. The nominal fill volume and overfill volume of ISO 10R glass vials by comparison is 10 mL and 13.5 mL, respectively. Conformance to the ISO standards enables the seamless transition from 10R glass vials to SiO₂ hybrid vials on liquid fill-finish and lyophilization manufacturing lines. Additionally, any automated equipment designed to handle ISO 10R glass vials will also be able to handle the SiO₂ hybrid vials without any adjustments.

Engineering a Hybrid Vial for Lyophilized Drug Formulations

Improved Heat Transfer and Batch Consistency

Heat transfer and sublimation are two fundamental transport phenomena for consistent lyophilized drug quality. Liquid formulations are first frozen by transferring heat across the vial

bottom. This is followed by slightly heating the frozen formulation in a partial vacuum to remove ice as water vapor, which is called sublimation. The rate of heat flow, or thermal conductivity, through the vial bottom and wall has a direct impact on both freezing and sublimation rates. Borosilicate glass has a thermal conductivity of 1.4 W/m K. This is higher than most common polymers (i.e., 0.1-0.6 W/m K), which are generally less effective at conducting heat.

SiO₂ hybrid vials are composed of a hybrid construction of plastic and glass materials, but the plastic constitutes about 99.993% of the mass and the rest glass. Heat transfer, therefore, is dominated by the plastic, which in this case is a cyclic olefin polymer with a thermal conductivity of 0.16 W/m K.²² If heat transfer is too restricted, the overall lyophilization time and the quality of the freeze-dried drug could be negatively impacted. Standard vials, irrespective of plastic or glass, have a conical indentation on their base, which restricts heat transfer to the shelf. One way of improving heat transfer in SiO₂ hybrid vials is to change the geometry of the SiO₂ hybrid vial base so that it makes more intimate contact with the shelf inside the lyophilization chamber.

SiO₂ hybrid vials were molded with a flat bottom, as shown in Figure 1, to improve heat transfer. A prior research collaboration with the University of Colorado in Boulder showed a 12% increase in the calculated heat transfer coefficient between a conical and flat-bottom SiO₂ vials.²³ This improvement enabled lyophilization processing times comparable to borosilicate vials with only minor adjustments to the process parameters, such as shelf temperature during primary drying. Millrock Technology conducted their own independent assessment and identified additional process adjustments to achieve similar results, which will be discussed later in this paper.

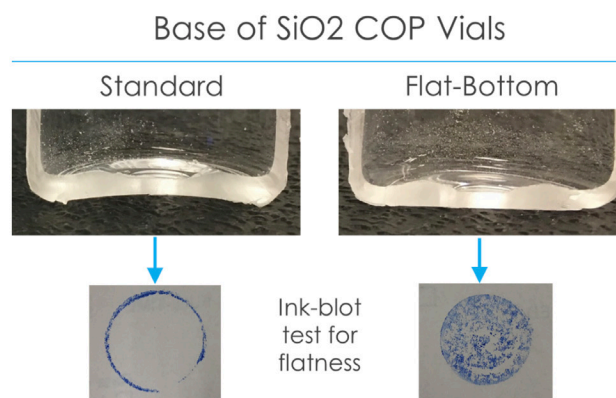


Figure 1. Cross-section and ink-blot test on the base of a standard COP vial (Left) compared to a flat-bottom vial (Right).

Reducing heat transfer variability among hundreds or thousands of vials within a batch is critical for ensuring consistent lyophilized drug product quality. Freezing and drying rates can vary over a batch due

to inconsistent heat transfer. The vial with the slowest heat transfer will be the last to completely dry, which will determine the total lyophilization process time. One way of minimizing this problem is tighter control over the physical dimensions of each vial in a batch. Tighter dimensions result in less vial-to-vial mass and wall thickness variability, which reduces heat transfer variability.

SiO₂ vials were molded within dimensional tolerances that are 3-5 times lower than standard borosilicate glass vials. This was shown to result in more consistent vial-to-vial heat transfer and drying rates during primary drying of 240 10mL SiO₂ hybrid vials compared to borosilicate glass.²³

Eliminating Wall Residue

Some liquid formulations wick up the walls of borosilicate glass vials and freeze as a white hazy deposit or residue. This can also happen if the liquid splashes up onto the wall prior to freezing. The combination of capillary forces and the water-loving or hydrophilic surface of glass are the root cause of wall residue. It is not only aesthetically unattractive but can be considered a quality inspection problem that can result in rejects and lost product.

The inner wall of a SiO₂ hybrid vial is covered with a water-repelling or hydrophobic coating. The polymer does not make direct contact with the drug formulation. The coating is composed of three layers with a pure silica glass (SiO₂) layer sandwiched between two layers of organosiloxane. This form of organosiloxane is chemically inert, hydrolytically stable, and free of leachables. The patented composition consists of silicon, oxygen, carbon and hydrogen atoms.²⁴ The presence of carbon and the absence of hydrophilic chemical groups results in a hydrophobic surface that eliminates wall residue as shown in Figure 2.

The hydrophobic wall characteristics also improved the ability to recover the reconstituted drug formulation by as much as 4% compared to a borosilicate glass vial. This minimizes needless waste of valuable drug or vaccine.

Ending Breakage

Borosilicate glass breakage has been an omnipresent problem with primary containers for liquid drug formulations.⁴ It is probably not surprising that breakage, albeit infrequent and unpredictable, can also occur during lyophilization of drug formulations.^{8,9}

SiO₂ has reported on the superior mechanical properties hybrid primary containers that practically eliminates breakage for liquid formulations.^{14,15} The combined ductility, heat deflection and impact strength of the COP polymer is responsible for SiO₂ hybrid vial toughness and resistance to breakage. These properties help to resist deformation and shrinkage over a wide temperature range and enables cold storage down to -196°C and steam sterilization at 121°C. The coating on the inside of the container is protected by the polymer, but also engineered to withstand mechanical abuse and thermal shock. Studies have shown no indication of damage, delamination or change in barrier performance.^{14,15}

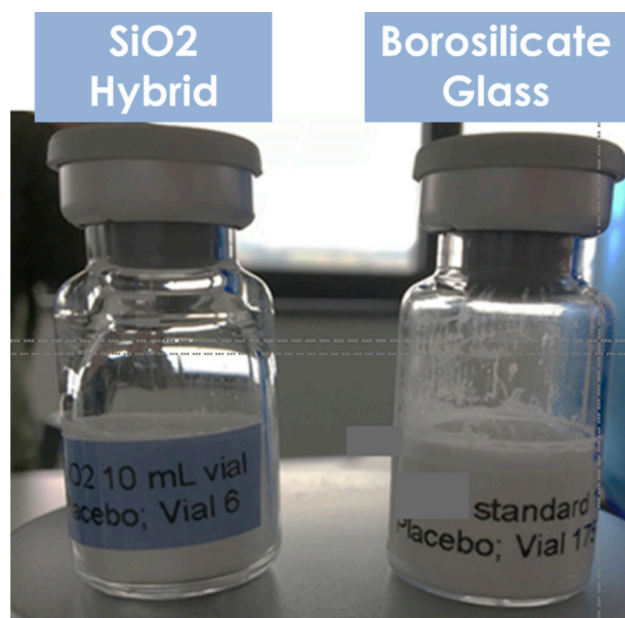


Figure 2. Picture of 10 mL SiO₂ hybrid vial (left) and a 10R borosilicate glass 10mL vial (right) after lyophilization of a placebo formulation. The glass vial shows white residue on the walls, but the SiO₂ vial walls is clear.

A preliminary breakage study was performed by the University of Colorado in Boulder on SiO₂ hybrid vials.²³ This study showed that more than half of borosilicate glass vials shattered upon lyophilization of a 10% weight/volume mannitol formulation at 80% nominal fill volume. None of the SiO₂ hybrid vials shattered or exhibited any signs of fracture. A more comprehensive investigation of breakage was conducted by Millrock Technology, which is discussed in a later section of this paper.

Observations and Considerations during Lyophilization

The primary objective of lyophilization, or freeze drying, is to create a product with consistent and desirable quality attributes. Achieving this objective requires that the product be processed below its critical temperature for the duration of the primary drying phase. The product temperature is controlled indirectly by controlling the shelf temperature and the chamber pressure, which determine the dynamics of sublimation within the vial. The ideal set of run conditions (i.e., shelf temperature and chamber pressure), which are specific to the product formulation, vial, and freeze dryer, is known as the design space.²⁵

The type of vial has a direct impact on the heat transfer dynamics during the freeze-drying process.²⁶ Understanding these dynamics is critical to develop an efficient and effective freeze-drying cycle. Whenever a vial is changed it is good practice to develop a new protocol that will ensure the product will be safely and efficiently lyophilized. When

considering a vial that is predominantly constructed from a polymer, the primary impact to the lyophilization process is the difference in heat transfer from the shelf to the product and how that effects the freeze-drying protocol. The proper approach to the change from a borosilicate glass to polymer-based vial is to understand the differences in heat transfer between the two types of vials. Once the heat transfer properties are determined, the information can be used to adjust the shelf temperature and chamber pressure to optimize the lyophilization process. This in essence means that a proper design space should be constructed for each type of vial. The goal of this investigation was to determine and compare the design space for both a borosilicate glass and cyclic olefin polymer vial for a 5% w/v sucrose solution.

A design space that defines the acceptable shelf temperature and product chamber pressures can be constructed using one-dimensional heat and mass transfer equations which relate the process conditions to the resulting product temperature and sublimation rate. The goal here is to determine the conditions that will yield the highest sublimation rate while also maintaining the product temperature below its critical temperature. Two process parameters that are necessary for these equations are the heat transfer coefficient between the vial and the shelf and the product cake resistance.²⁷

The heat transfer coefficient (K_v) of the vial determines the rate of heat transfer between the shelf and product under a given temperature difference. This is expressed by the following equation:

$$dQ/dt = K_v \cdot A_v \cdot (T_s - T_b) \quad (1)$$

where dQ/dt is the heat flow into the vial, K_v is the vial heat transfer coefficient, A_v is the area of the bottom of the vial, and T_s and T_b are the shelf and product temperatures, respectively.²⁷

The product cake resistance (R_p) is an expression that represents the resistance to water vapor flow by the dried layer of the product, and is expressed in the following equation:

$$dm/dt = (A_p \cdot (P_i - P_c)) / R_p \quad (2)$$

where dm/dt is the rate of sublimation, R_p is the product cake resistance, A_p is the area of the product surface in the interior of the vial, and P_i and P_c are the pressure of the sublimation interface and the product chamber, respectively.²⁷

During the steady-state period in primary drying, it can be assumed that all the heat that enters the vial, expressed in Eq. 1, is used for sublimation according to the following equation:

$$dQ/dt = \Delta H_{SUB} \cdot dm/dt \quad (3)$$

where ΔH_{SUB} is the latent heat of sublimation, with a value of 2834 J/g used in this study.^{27,28}

The K_v of a vial system is dependent on the specific vial and freeze dryer. It is also heavily influenced by the pressure within the product chamber. At higher pressures, the rate of heat flow via gas conduction between the bottom of the vial and the shelf increases. The relationship between the heat transfer coefficient and the chamber pressure is expressed by the following equation:

$$K_v = K_c + (K_p \cdot P_c) / (1 + K_o \cdot P_c) \quad (4)$$

where K_c , K_p , and K_o are all coefficients that are experimentally fit to K_v versus P_c data. This allows K_v to be extrapolated and estimated across a wider range of pressure than is necessary to experimentally test and is important for developing an accurate design space.²⁷

The cake resistance tends to increase throughout the primary drying phase as the length of the dried layer increases, and can be expressed by the following equation:

$$R_p = R_{p_0} + (A_1 \cdot L) / (1 + A_2 \cdot L) \quad (5)$$

where L is the length of the dried product cake above the sublimation interface and R_{p_0} , A_1 , and A_2 are coefficients that are experimentally fit to R_p vs. L data.²⁷ Due to inaccuracies with thermocouple measurements at the end of primary drying, it is difficult to measure the cake resistance.²⁹ Instead, Eq. 5 can be used to calculate the maximum cake resistance at the end of primary drying when the length of the dried cake is equal to the fill height of the solution. It is at this point that the product temperature is typically at its highest point and therefore the highest risk to the product. Therefore, the design space is determined to process the product safely and efficiently with this maximum R_p taken into consideration.

Heat Transfer Coefficient (K_v) Determination

The first part of the design space investigation was to determine the heat transfer coefficient for each vial type within a freeze dryer. A comparison was made between 10 mL SiO₂ flat bottom hybrid and 10R borosilicate glass vials. The vial heat transfer coefficient is not dependent on the formulation within the vial,²⁹ therefore a 5% w/v mannitol solution was used to determine the vial heat transfer coefficients across a range of pressures, namely 50 mTorr, 100 mTorr, and 150 mTorr. An array of 19 vials of each vial type were frozen to -40°C and then dried at -20°C in a MicroFD® freeze dryer. An AccuFlux® heat flux sensor with LyoPAT® software was used to measure the heat flow into the vials and directly calculate the vial heat transfer coefficient at each pressure for each vial. The results of these tests in

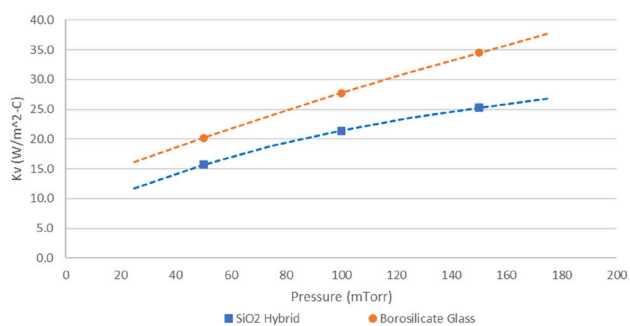


Figure 3. Plot of measured heat transfer coefficient (K_v) for 10 mL SiO₂ hybrid vial (blue, square) and 10R borosilicate glass vial (orange, circle). The dotted trend lines are fit to Equation 4 for each vial type.

Figure 3 show that on average, the heat transfer coefficient for the SiO₂ hybrid vials is approximately 24% less than the heat transfer coefficient for the borosilicate glass vials.

Cake Resistance (Rp) Determination

Once the vial heat transfer coefficient is known the only missing piece of information needed to create the design space is the maximum product cake resistance. The maximum product cake resistance is found at the end of the primary drying phase, shortly before the end of sublimation. The dried cake length is at its maximum at this point. The pressure at the sublimation interface and product temperature at the bottom of the vial are also at their maximum.

For this study, a volume of 3.8 mL (i.e., 38% fill volume) of a 5% w/v sucrose formulation was filled into both the 10 mL SiO₂ hybrid vials and the 10R borosilicate glass vials to produce a total fill height of approximately 1 cm. To reduce variation in the frozen cake structure between vials and between batches and vial types, all vials were first frozen to -50°C, then annealed at -10°C for two hours before re-freezing to -50°C and proceeding with primary drying. An array of 19 vials of each type were freeze-dried in separate cycles in a MicroFD with a shelf temperature of -20°C and a chamber pressure of 75 mTorr. An AccuFlux heat flux sensor with LyoPAT software was used to measure the heat flow into the vials and directly calculate the sublimation rate, which was then used to calculate the product cake resistance throughout the primary drying phase. The calculated product cake resistance values during approximately the first 40% of primary drying were then used to fit the coefficients of Equation 5 and extrapolated to the maximum cake resistance at a maximum cake length of 1.0 cm (Figure 4).

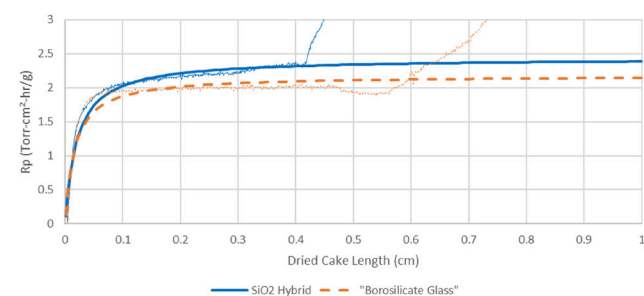


Figure 4. Plots of measured product cake resistance for 10 mL SiO₂ hybrid vial (blue, solid) and 10R borosilicate glass vial (orange, dashed). The measured values are shown as narrow lines and the trend lines fit to Eq. 5 are shown in bold.

Design Space

Once the heat transfer coefficient was known across several pressures and the product cake resistance was known at its maximum value, a design space for a given formulation, vial type, and freeze dryer

combination can be created. The design space was created by combining equations 1, 2, and 3 and solving for the resulting sublimation rate at a given pressure along several separate shelf temperature and product temperature isotherms.²⁷ The design space for the 10R borosilicate glass vials and the 10mL SiO₂ hybrid vials with a 5% sucrose solution are shown in Figures 5 and 6, respectively. The acceptable control region within the design space is shown as a yellow triangle. The boundary of the control region is defined by the equipment capability line and by the product temperature isotherm corresponding to the critical temperature of the product. The product temperature isotherm is typically taken with a safety offset from the solution's critical temperature, therefore in Figures 5 and 6 the acceptable control region is limited by the -34°C product temperature isotherm, which is offset by 2°C from the solution's reported critical temperature of -32°C. Conditions outside of this region will yield

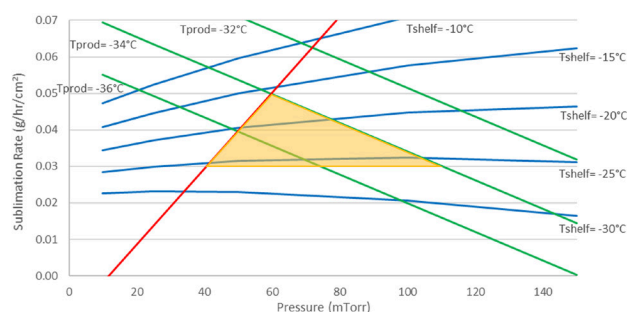


Figure 5. Design space for 10R borosilicate glass vials with 5% sucrose solution. Acceptable control region shown as a yellow triangle. The shelf temperatures, equipment capability and the product temperature isotherms are shown as blue, red, and green lines, respectively.

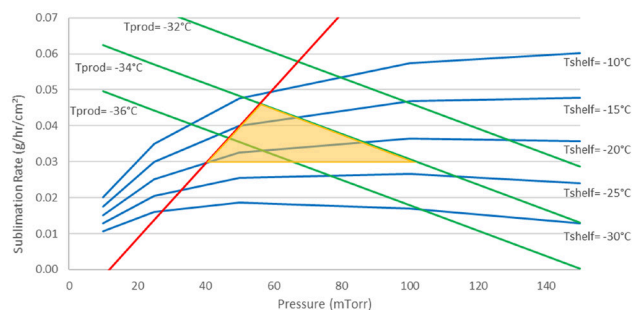


Figure 6. Design space for 10 mL SiO₂ hybrid vials with 5% sucrose solution. Acceptable control region shown as yellow triangle. The shelf temperatures, equipment capability and the product temperature isotherms are shown as blue, red, and green lines, respectively.

either a sublimation rate that exceeds the sublimation rate limit through the vapor port of the freeze dryer or a product temperature that exceeds the critical temperature, leading to product cake collapse or degradation.

Within the acceptable control region of the design space, conditions can be found and selected that will yield the highest sublimation rate, and therefore the shortest primary drying duration. A comparison of the borosilicate glass vial and the SiO₂ hybrid vial design space shows that both vials can be used to develop a lyophilization cycle with similar sublimation rates, and therefore similar primary drying times. In this specific case, the maximum attainable sublimation rate in the borosilicate glass vials is approximately 0.050 g/hr/cm² at a shelf temperature of approximately -16°C and chamber pressure of 60 mTorr. This compares closely with the maximum sublimation rate in the SiO₂ hybrid vials, which is approximately 0.046 g/hr/cm² at a shelf temperature of -12°C and a chamber pressure of 60 mTorr. In general, the design space for the SiO₂ hybrid vials shows that the lower vial heat transfer coefficient can be compensated with a higher shelf temperature to achieve similar sublimation rates as the borosilicate glass vials.

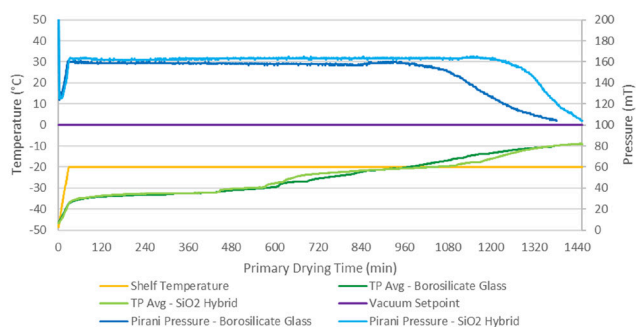


Figure 7. Primary drying comparison between borosilicate glass vials and SiO₂ hybrid vials, showing product temperature (green lines) and Pirani pressure (blue lines) throughout primary drying. The steeper convergence of the Pirani reading for the SiO₂ hybrid vials (light blue) indicates a more uniform sublimation rate across the batch of vials.

Advantages for the End-User – More Consistent Drying Across a Batch

Throughout the process of determining the design space additional observations were made relating to the overall freeze-drying process in both vial types. Most notably, during primary drying the SiO₂ hybrid vials sublimated more uniformly than the borosilicate glass vials, as indicated by both the measured heat flux and the convergence between the Pirani gauge and capacitance manometer. The pressure measurement from the Pirani gauge is affected by the presence of water vapor in the chamber and reads higher than the

vacuum setpoint. The end of primary drying can be detected when the Pirani gauge pressure converges to the control pressure at the vacuum setpoint. The onset of the convergence represents the point at which most of the vials have completed sublimation, and the offset of this convergence is when all the vials have completely sublimated. In Figure 7, the amount of time for the Pirani gauge to converge for the borosilicate vials is about twice the time for the hybrid vials. This indicates that the sublimation rate across the batch in the hybrid vials is more uniform compared to glass vials. In other words, all the SiO₂ hybrid vials reached the end of sublimation within a shorter time than in the batch of glass vials. This can likely be attributed to the much smaller dimensional variations and thus heat transfer variation of the SiO₂ hybrid vials compared to the glass vials.

Advantages for the End-User – Less Breakage at Higher Fill volumes

Vial breakage is a problematic occurrence during lyophilization that can lead to significant loss of production time and product. A study was conducted to compare the rate of vial breakage between 10R borosilicate glass vials (Schott TopLine) and 10ml flat-bottom SiO₂ hybrid vials under different fill volumes of a 10% w/v solution of mannitol. A selection of both the borosilicate glass and the SiO₂ hybrid vials were filled with a 10% w/v mannitol solution and processed under lyophilization conditions to test for vial breakage. Groups of vials were filled with volumes of 4, 6, 8, and 10mL, representing a fill percentage of 40, 60, 80, and 100% of the nominal fill volume.

The lyophilization cycle consisted of rapid freezing followed directly by primary drying. The shelves were cooled to -40°C at a rate of 1°C/min and held for two hours to freeze the vials, and then the chamber pressure was reduced to 150 mTorr and the shelf was warmed to 5°C at 0.5°C/min. After the vials completed primary drying, they were removed from the lyophilizer and inspected.

The glass vials had breakage failures, shown in Table 1, at almost every fill volume, with a higher rate of failure at higher fill volumes. The SiO₂ hybrid vials did not have any failures at any fill volume and did not indicate any visual signs of stress cracking. Overall, the glass vials broke at higher frequency with a higher fill, and the SiO₂ vials did not break at all, regardless of the fill volume. All of the broken glass vials were observed to have broken by shattering, with no observation of a ‘lensing’ break as shown in Figure 8. The SiO₂ hybrid vials were thoroughly inspected and no evidence of stretching, cracking, or any other stress was visible. The results of this study demonstrate the

Fill Volume (mL)	Fill Percentage (%)	Borosilicate Glass		SiO ₂ Hybrid	
		# Broken	%	# Broken	%
10	100	4/12	33	0/16	0
8	80	5/27	19	0/37	0
6	60	1/38	3	0/38	0
4	40	0/35	0	0/38	0

Table 1. Breakage results for 10R borosilicate glass and 10mL SiO₂ hybrid vials at different fill volumes.

Borosilicate Glass Vials



SiO₂ Hybrid Vials



Figure 8. Images of broken borosilicate glass vials and unbroken SiO₂ hybrid vials following typical freeze-drying cycle with 10% w/v mannitol. Vials are depicted with an 8mL (80%) fill volume.

superior durability of the SiO₂ hybrid vials compared to borosilicate glass vials.

Summary

An investigation was conducted to compare the differences in heat transfer between the borosilicate glass vials and SiO₂ hybrid vials. The resulting lyophilization process design spaces generated from these results showed that the lower inherent heat transfer of the SiO₂ hybrid vials is not a restricting factor for designing a safe and efficient lyophilization cycle. Comparable lyophilization cycles with similar sublimation rates were achieved using both types of vials.

Furthermore, vial breakage rates across a range of fill volumes demonstrated a clear advantage of the SiO₂ hybrid vials over borosilicate glass vials. The use of the SiO₂ hybrid vials eliminates the problem of vial breakage even at 100% of nominal fill volumes. This opens the potential for pharmaceutical companies to produce a higher number of doses per vial using a smaller vial for the same dosage. This enables the number of doses processed to be dramatically increased. Lastly, more uniform sublimation or drying was observed across a batch of lyophilized product in SiO₂ hybrid vials compared to glass vials. This may result in more consistent product quality within a batch and between batches.

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