Alternative for SARS-CoV-2 Vaccine Primary Package Systems: Daikyo Crystal Zenith® Cyclic Olefin Polymer Vials

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Abstract

For primary package systems for SARS-CoV-2 vaccines, vials based on Daikyo Crystal Zenith® cyclic olefin polymer (COP) are a potential alternative to glass vials. COP vials have low levels of extractables, potential low levels of interaction with vaccines, and very good resistance to breakage. Permeability of oxygen and carbon dioxide has been quantified from room temperature through cryogenic temperature – enabling risk assessment and judgment if a COP-based system can meet the maximum allowable leakage limit (MALL) for a vaccine. COP vials are compatible with elastomer stoppers with FluroTec® film. They are approved world-wide for drug products comprising monoclonal antibodies, proteins, peptides, small molecules, and gene therapies.

Background

A challenge in the distribution of a SARS-CoV-2 vaccine concerns storage, namely selection of a vial/stopper primary package system that guarantees quality and safety from manufacture through delivery. This selection challenge, which is complicated by accelerated timelines for vaccine approval, results from:

1. Vaccine Platform. Six platforms are considered; they are listed with their proposed vehicles in Table 1. (1) Noteworthy is that two (RNA, DNA) are new. Ordinarily, there would be no difficulty in selecting a package system for any of the platforms, since ample time would be available for evaluation of compatibility with both vaccine and vehicle. But, for a SARS-CoV-2 vaccine this is not the case, since approval timelines are accelerated. So, whether the vaccine platform is extant or new, selection of the package system must be made quickly.
2. Suitability and Availability. Once a package system is demonstrated compatible with a vaccine and vehicle, other factors must be considered, such as:
    - stopper design/performance
    - storage temperature: room (25°C), refrigerated (2-8°C), ultra-low (-80°C), or cryogenic (-180°C)
    - component availability

The issues of stopper design/performance and storage temperature have been discussed prior. (2) This article considers the issue of component availability as it relates to vials. Typically, primary package systems for vaccines employ glass vials. But, with the increased demand resultant from

the SARS-CoV-2 pandemic, potential glass vial shortages and unacceptable lead times must be anticipated. In view of this, polymer vials as an alternative should be considered.

Table 1. Potential Vaccines for SARS-CoV-2 (1)

Vaccine Platform	Chemical Composition	Vehicle	Existing, Licensed Human Vaccine
RNA	nucleotides (ribose groups, amino/amide groups, charged phosphate groups)	encapsulated in lipid in non-polar liquid	No
DNA	nucleotides (ribose groups, amino/amide groups, charged phosphate groups)	aqueous (saline) solution, encapsulated in lipid in non-polar liquid	No
Recombinant Protein	polypeptides (amino acid groups)	aqueous	Yes (baculovirus and yeast expression)
Viral Vector Based	virus shell comprises proteins (i.e., polypeptide: amino acid groups)	aqueous	Yes (vesicular stomatitis virus)
Live Attenuated	virus shell comprises proteins (i.e., polypeptide: amino acid groups)	aqueous	Yes
Inactivated	virus shell comprises proteins (i.e., polypeptide: amino acid groups)	aqueous	Yes

Cyclic Olefin Polymer Vials

A primary package system must be fit-for-purpose, i.e., compatible with drug product and able to provide protection through shelf life. A key requirement of a vial (glass or polymer) for such a system is transparency, so drug product may be inspected. There are many commercially-available transparent polymers, such as poly(ethylene terephthalate) (e.g., beverage bottles). Among them, the best choice for a vial is Daikyo Crystal Zenith® cyclic olefin polymer (COP). COP has the best overall combination of properties, namely resistance to permeation (air/water) and potential compatibility (i.e., inertness toward) with drug products (3).

COP vials and syringes have become widely accepted over the past 20 years. They are approved by regulatory bodies for drug products comprising monoclonal antibodies, proteins, peptides, small molecules, and gene therapies.

This article discusses the performance of Daikyo Crystal Zenith® COP vials and offers why they can be an alternative to glass vials for primary package systems for vaccines.

COP Chemistry

Synthesis of COP, shown in Figure 1, employs a novel polymerization method: ring opening metathesis polymerization. This method was discovered in the 1970's and was the basis of the 2005 Nobel Prize in chemistry. (4) Synthesis of COP requires two steps, polymerization followed by hydrogenation.

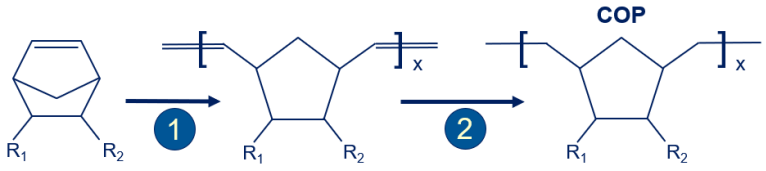

Figure 1. Synthesis of Cyclic Olefin Polymer (COP) from Norbornene. 1. ring-opening metathesis polymerization. 2. hydrogenation

Extractables and Leachables

An area where Daikyo Crystal Zenith® COP has inherently good performance is extractables and leachables (E&L). An E&L study is performed on a package system component to identify elements/compounds that may migrate from component into drug product, in particular those that may put patient safety at risk. The first phase is the extractables evaluation. This employs accelerated conditions to cause migration of any compound that possibly could appear in the drug product. Results inform the subsequent leachables study.

For glass and COP vials, the extractables evaluation process consisted of sectioning the samples (to maximize surface area), immersion in a selected liquid media at elevated temperature for a fixed time, and analysis of resultant media by chromatographic and mass spectrometric methods. As anticipated, extractables analysis of glass and COP vials revealed differences. Results for various Type 1B glass vials revealed that numerous elements can be observed at levels ≥ 0.01 μg per g sample: e.g., B, Ca, As, and Ba. Results for COP vials revealed only the presence of a small number of low molecular volatile organic compounds, such as 2-ethyl-1-hexene, at levels ≥ 0.01 μg per g sample. No inorganic element was observed. This was expected; COP comprises essentially only carbon and hydrogen.

With few extractables, and those extractables being present at low levels, COP vials present a low risk for leachables that might interact with vaccine and put patient safety at risk. Thus, they can be considered a potential alternative to glass vials.

Interaction with Drug Product

Polymers, in general, have a much lower surface energy than glass or silicon dioxide (5,6):

- glass (typical): ~ 80 mJ/m^2
- cyclic olefin polymer: ~ 40 mJ/m^2
- SiO_2 ~ 280 mJ/m^2

A drug product is more likely to be attracted to, interact with, and adhere to, high-surface-energy materials. This can cause: (a) adsorption of the drug product to the container, thereby reducing dosage, (b) unwanted chemical change in the drug product, or (c) formation of particles, possibly causing immunogenetic effects. (7,8) These phenomena have been reported. (9-12)

Interactions with glass and Daikyo Crystal Zenith® COP have been examined at West – with a focus on formation of particles. (13) Vials (2 mL), filled with solutions of simulated drug products, were subjected to agitation (orbital shaker, 200 rpm, 4 days, room temperature). Analyses of resultant solutions are given in Table 2. For each, COP vials showed fewer particles, lower levels of turbidity, and better product recovery. Data clearly indicate less interaction of simulated drug product with COP.

Table 2. Levels of Particles, Turbidity, and Recovery Resultant for Simulated Drug Products after Agitation. Particle level was measured by dynamic fluid imaging, protein recovery was measured by size exclusion high performance liquid chromatography, and turbidity was measured by light obstruction (350 nm). (13)

	mAb – 1		mAb – 2		mAb – 3		mAb – 4		mAb-5	
	Glass	COP	Glass	COP	Glass	COP	Glass	COP	Glass	COP
Particles (per ml)	36 K	18 K	750	700	325 K	165 K	9 K	1 K	9 K	4 K
Turbidity	1.4	0.4	0.05	0.003	2.4	1.5	0.48	- 0 -	0.21	0.01
Recovery (%)	75	95	90	100	10	68	90	100	90	98

Based on both the literature reports noted above and this work, risk of interaction with vaccine could well be lower for COP vials than for glass vials. Thus, COP vials can be considered a very good potential alternative to glass vials.

Note that since SiO_2 has a much higher surface energy than glass, under similar conditions interactions with vaccines might be much higher than observed with glass. Thus, vials comprising SiO_2 may not be a good alternative.

Mechanical Properties

Almost all polymers perform better than glass in terms of fracture resistance. This is common knowledge, and certainly true in the case of Daikyo Crystal Zenith® COP. In Figure 2 is shown the fracture resistance of COP vials and several commercial glass vials. (14) In this regard, COP vials are a better option than glass vials, and may be suited to lyophilized vaccines. (15)

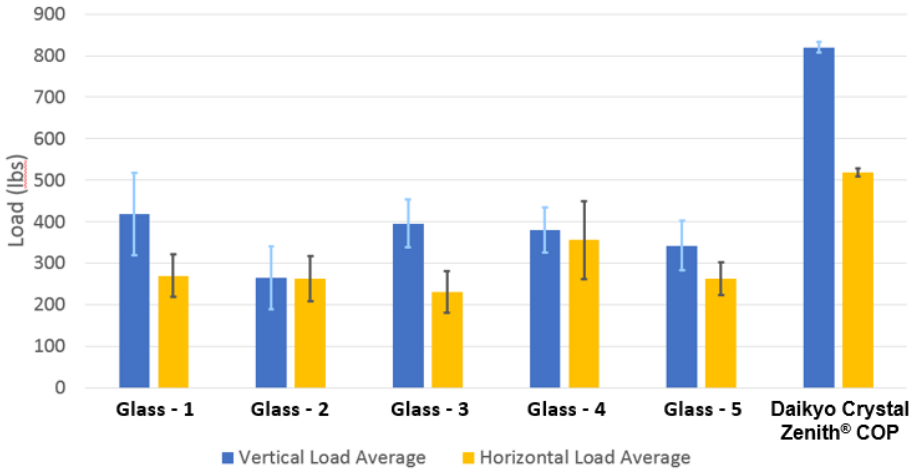

Figure 2. Load Required to Cause Fracture of 2 mL Glass and COP Vials (14)

Container Closure Integrity and Permeability

An area where glass exceeds all polymers in performance is permeability. All polymers are permeable; glass is not. (16) This point relates to the primary package system's ability to provide container closure integrity (CCI), in other words the ability to meet the requirements of the maximum allowable leakage limit (MALL) for the vaccine. MALL is discussed in detail in United States Pharmacopeia Chapter <1207>. (17) Even though Daikyo Crystal Zenith® COP vials do not have the same resistance to permeation as glass vials, that does not necessarily mean unsuitability. Each situation must be assessed in view of the MALL for the vaccine. Quantification of permeability enables this assessment, and determination if a COP vial package system of a given size (matching stoppers/seals are established) is suitable.

In Figure 3, the permeability of COP vials to oxygen is shown. (14) Package systems were filled with nitrogen and stored in air. Rate of permeability of oxygen decreases with temperature, as expected. In fact, the permeability rate at -80°C is very similar to that observed for glass vials. From these data, rates of oxygen ingress can be determined. For example, at room temperature, rate of oxygen ingress is only approximately 0.04% per hour.

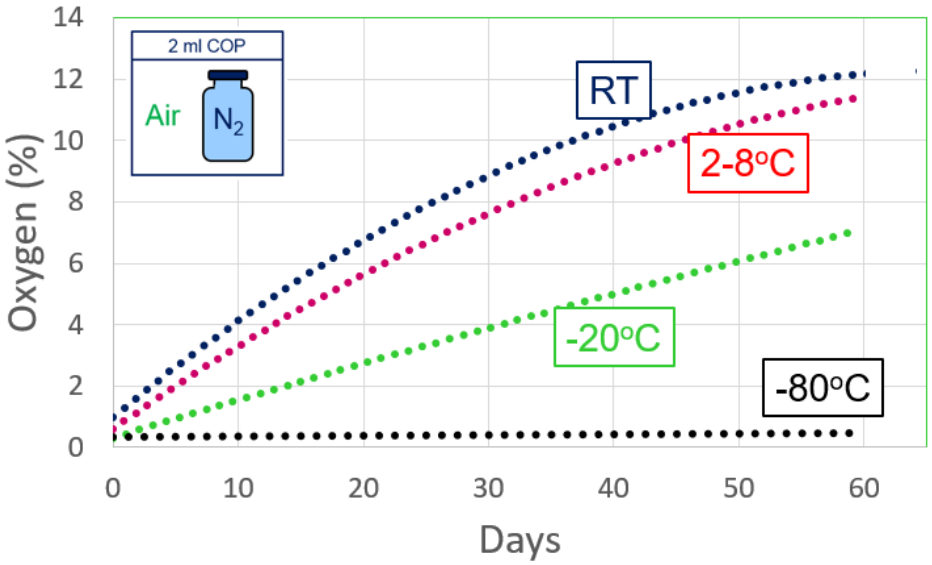

Figure 3. Oxygen Concentration vs Time and Temperature for 2 mL Daikyo Crystal Zenith® COP Vial Primary Package Systems. Elastomer stoppers were NovaPure® 1358 / 4023/50 Gray (i.e., with FluroTec® barrier film). Measurement was by frequency modulated spectroscopy headspace analysis. (14)

In Figure 4, the permeability of COP vials to oxygen at cryogenic temperature (-180°C, i.e., vapor of liquid nitrogen) is shown. Package systems were filled with air and stored in the vapor of liquid nitrogen. COP vials show excellent performance, no gas exchange at all, as evidenced by no change in oxygen level.

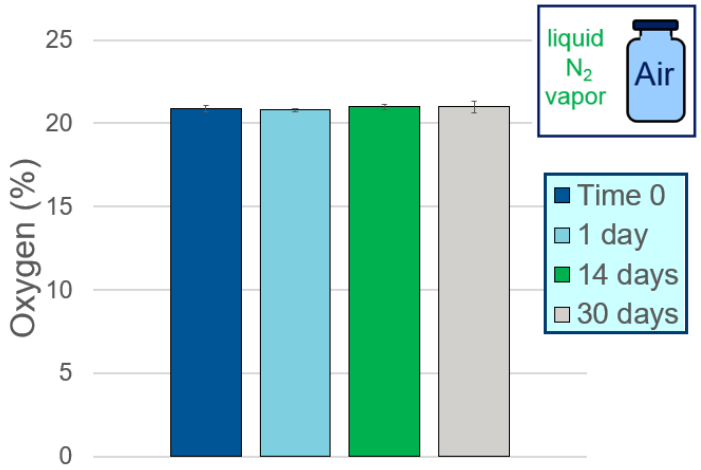

Figure 4. Oxygen Concentration vs Time for 2 mL Daikyo Crystal Zenith® COP Vial Primary Package Systems at -180°C. Elastomer stoppers were NovaPure® 1358 / 4023/50 Gray (i.e., with FluroTec® barrier film). Measurement was by frequency modulated spectroscopy headspace analysis.

Another aspect to consider is ingress of carbon dioxide resultant from storage/shipment on dry ice (i.e., solid carbon dioxide, -78°C). It has been reported that COP vials can absorb some carbon dioxide during dry ice storage exposure, and that this absorbed carbon dioxide can desorb into the package system upon warming.

As was the case with oxygen, the presence of carbon dioxide does not necessarily mean that a COP vial package system is unsuitable. The key is to quantify the permeability, so that a risk assessment can be made. See Figure 5, where 5 mL COP vial package systems, filled with air, were stored in dry ice for up to seven days. Upon removal and storage at room temperature, levels of carbon dioxide were measured. Note there is only a very small amount of ingress. For example, after three days (common for shipment), and 30 minutes at room temperature, there is no observable carbon dioxide, and after three days only 1% carbon dioxide (a rate of 0.01% per hour). Moreover, systems stored in a secondary container (heat-sealed, three-layer polyester-based bag, common for food storage) showed no ingress; this should provide a solution for a vaccine that cannot tolerate carbon dioxide exposure. (14)

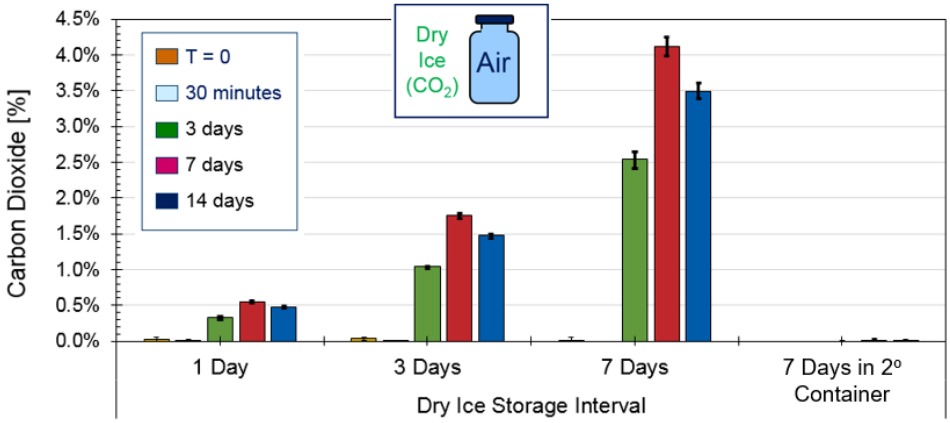

Figure 5. Carbon Dioxide Concentration vs Time for 5 mL Daikyo Crystal Zenith® COP Vial Containment Systems after Storage in Dry Ice (-78°C) and Storage in Air (room temperature). Elastomer stoppers were 20mm NovaPure® 1343 / 4023/50 Gray (i.e., with FluroTec® barrier film). Measurement was by frequency modulated spectroscopy headspace analysis. (14)

Knowing the rate of ingress of gas versus time and temperature enables the risk assessment needed to determine if a Daikyo Crystal Zenith® COP vial package system is suitable for a vaccine.

Summary

Daikyo Crystal Zenith® COP vials are potentially a good alternative to glass vials for primary package systems for SARS-CoV-2 vaccines. Levels of extractables are low, potential interaction with vaccines could well be low, and fracture resistance compared to glass is better. Permeability by oxygen and carbon dioxide, from room temperature through cryogenic temperature, has been quantified. This enables a risk assessment and judgment if a COP-based system can meet the MALL for a vaccine. COP vials are compatible with elastomer stoppers with FluroTec® film.

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