Cyclic Olefin Polymer – Advantages versus Glass for Parenteral Drug Packaging/Delivery – a Brief Analysis

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I. Summary
For storage/delivery of parenteral drug products, polymers have many advantages over glass, based upon:
• composition
• surface chemistry
• physical properties (risk of delamination)
• modulus/strength/brittleness
• performance at low temperature
• manufacturing

Among polymers, cyclic olefin polymer (COP) (Daikyo Crystal Zenith® product) is the best choice, based upon:
• transparency
• resistance to oxygen/water
• compatibility with multiple drug products (i.e., lack of interaction)

II. Introduction
Historically, glass has been used in vials/syringes/cartridges for the storage/delivery of drug products. The recent trend has been to replace glass with polymers. This paper discusses the benefits of polymers on the basis of chemistry, physical properties, and manufacturing – and demonstrates that among polymers – the best choice is poly(norbornene) (Daikyo Crystal Zenith® cyclic olefin polymer).

III. Polymer vs. Glass

Chemistry – Composition
Pharmaceutical glass is typically Type I borosilicate - comprising approximately seven oxides (e.g., Na₂O), the cations of which could leach into a drug product and induce diminished/deleterious effects, which is especially problematic for biologic drug products. In contrast, polymers comprise typically only carbon and hydrogen, and thus intrinsically, risk of a leachate causing an issue is reduced substantially.
Chemistry - Surface
Interaction of drug product with a leachate is not the only concern as interaction with a container can also occur. Low surface energy materials (e.g., protein drug products) are attracted to, and adhere more strongly to, high surface energy materials (e.g., glass), but adhere much less so to low surface energy polymers. This has been observed experimentally. (1) Stronger interaction increases the risk of alteration of drug product resultant from reaction with glass surface. Use of polymer lowers risk.

A second aspect of surface interaction relates to silicone oil. A low surface energy elastomer plunger will tend to adhere to the inside wall of a high surface energy glass syringe. To assist movement of the plunger in the syringe, a layer of silicone oil is placed on the inside of the syringe (this is done for almost all glass syringes). It is well known that silicone oil can cause alteration/denaturation of protein molecules that results in the formation of particulates, which is an unacceptable situation since particulates can result in diminished/deleterious effects. (1) A lower-risk solution is to employ a polymer-based syringe that has a lower surface energy and enables plunger movement without the need for silicone oil.

Physical Properties – Delamination
Glass undergoes the phenomenon of delamination – the release of very thin lamellar flakes of glass into adjacent solution. It is most likely to occur in high pH solutions (see the Figure). The process may result from the leaching of network-forming oxides (e.g., silicon oxide) from the surface, resulting in a weakened surface that enables subsequent lamellae removal. Delamination may result, more simply, from reaction of glass surface with (OH)\(^{-}\) ions – see Equation. (2)

\[
\text{Surface} - \text{O-Si-O} + \text{Na}^+(\text{OH})^{-} \rightarrow \text{Surface} - \text{OH} + \text{Na}^+(\text{O-Si-O})^{-}
\]

Either way, as a result, glass flakes can be found in drug products. Delamination is an extremely serious issue that can result in drug recalls. In fact, the U.S. FDA issued a specific notice concerning glass in 2011 (3), recapitulated here in part:

**Advisory to Drug Manufacturers: Formation of Glass Lamellae in Certain Injectable Drugs. [3-25-2011]**
The U.S. Food and Drug Administration is advising drug manufacturers of the potential formation of glass lamellae (glass fragments) in injectable drugs filled in small-volume glass vials. Several drugs have recently been recalled due to this problem. Glass has many advantages over other packaging materials, but one well-known disadvantage is the potential for glass under certain conditions to shed thin, flexible fragments called “glass lamellae.” These lamellae are shed from the interior surface of the glass container directly into the drug and are difficult to detect by visual inspection.

Figure. Delamination of Glass – Microscopic Examination. A. Type I borosilicate glass – untreated. B. Type I borosilicate glass – exposed to pH = 10 solution for 1 hour at 120 °C (notice the pitting).
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Further, USP has issued the guidance Chapter <1660> *Evaluation of the Inner Surface Durability of Glass Containers*, specifically dealing with delamination. From 2010-2016, FDA issued over 100 recalls for parenteral drug products due to delamination or particulates. (4)

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<tbody>
<tr>
<td>Recalls</td>
<td>8</td>
<td>12</td>
<td>12</td>
<td>28</td>
<td>24</td>
<td>13</td>
<td>12</td>
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For example, in 2010, all 2 mL and 10 mL vials of methotrexate product from a major supplier in the U.S. were recalled for glass delamination. Some manufacturers have addressed this by modified glass processing, e.g., Schott DC (delamination controlled) product. *Nevertheless, a more effective solution always will be elimination of the problem altogether, such as use of polymer, which is not susceptible to delamination.*

**Physical Properties – Modulus/Strength/Brittleness**
Glass has very high modulus and strength, but is also very brittle. Its impact resistance is only ~ 20 J as compared to ~ 550 J for polymer. Chances of glass breakage are substantially higher. In syringes, this has been demonstrated experimentally. Flange strength of syringes comprising glass is only ~ 50% of that of syringes comprising polymer [poly(norbornene)]. (5) *Polymer provides a much more durable product.*

**Physical Properties – Performance at Lower Temperatures**
Glass and elastomer are incompatible at low/cryogenic temperatures (ca. -80 °C to -180 °C) – which can be a critical consideration for storage of biologic drug products. The reason is the substantially different coefficients of thermal expansion (glass ~ 4 x 10⁻⁶ cm/cm-K, elastomer ~ 80 x 10⁻⁶ cm/cm-K). This difference can result in gaps between the elastomer component and container with concomitant risk of loss of container closure integrity. *In contrast to glass, elastomer and polymer materials shrink at comparable rates, substantially reducing risk of gap formation and loss of CCI.*

**Physical Properties – Permeability**
There is one area where glass performance cannot be matched or exceeded: permeability to water and oxygen. Glass is impervious to both. While polymers can have low values for permeability, they do not match glass, but other glass issues remain, as explained above. Of course, with polymer systems, any permeability issue can be mitigated with secondary containers.

**Manufacturing**
Polymers offer benefits in manufacturing. Glass vials/syringes/cartridges are made from melted glass – drawn tubing mechanically sealed/molded in melt phase. In contrast, polymer vials/syringes/cartridges are made by injection molding of melted polymer. Injection molding enables much higher precision since dimensions are controlled by machined metal mold fixtures. In the case of glass staked needle syringes, a tungsten probe is used to create an orifice for the needle, creating risk of contamination by tungsten. *Polymers offer better dimensional control and lower risk of contamination.*

IV. Selecting the Right Polymer

The benefits of polymers are clear. The question then is what is the right polymer for drug product packaging and delivery systems. Transparency is essential. Any vial/syringe/cartridge absolutely must be transparent to enable visual inspection of contents. Translucency is not sufficient. This narrows the choice considerably. Transparency alone, while necessary, is not singularly sufficient. A polymer must have other characteristics, namely:

1. good resistance to oxygen transmission
2. good resistance to water transmission
3. compatible with drug product (i.e., having no deleterious effect)
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for Parenteral Drug Packaging/Delivery – a Brief Analysis

Transparent, commercially available polymers are cited below. Only poly(norbornene) (i.e., COP) meets all three requirements:

<table>
<thead>
<tr>
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<th>$O_2$ Permeability (a)</th>
<th>Water Vapor Transmission Rate (b)</th>
<th>Comment</th>
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<tbody>
<tr>
<td>poly(norbornene) –</td>
<td>1.2</td>
<td>&lt; 10</td>
<td>contains only carbon and hydrogen – minimal risk of interaction with drug product – minimal extractables, no discernible elemental impurities – elongation-at-break ~ 20% - suitable for multiple sterilizations</td>
</tr>
<tr>
<td>Daikyo Crystal Zenith® cyclic olefin polymer (COP)</td>
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a. Barrer = $[10^{-11} \times (\text{cm}^3 \text{ (STP)}) \times \text{cm}] / [(\text{cm}^2) \times \text{seconds} \times \text{torr}]$
b. $(\text{grams – mm) / (m}^2 \text{ – day})$

- **Poly(ethylene terephthalate)** - excellent $O_2$ permeability (0.04) but a high level of water permeability (120) – suitable for soft drinks, but not drug products – under conditions of autoclave sterilization may produce phthalate compounds that are capable of being leached
- **Polycarbonate** – good $O_2$ permeability (1.4) but a very high level of water permeability (> 400)
- **Poly(methyl methacrylate)** – good $O_2$ permeability (1.2) but an extremely high level of water permeability (> 900)
- **Poly(vinylidene chloride)** – exceptional resistance to $O_2$ (0.005) and good resistance to water (10) – as evident by its historical use (now abandoned) as a food wrap – risk of HCl release during autoclave sterilization
- **Low-density polyethylene** – good $O_2$ permeability (2.2) and a moderate level of water permeability (~ 80), but not as good as poly(norbornene) – commonly employed as a thin wrap
- **Polyamide blend** (specialty) – issues exist – interaction of amide groups with protein drug products, and depolymerization via hydrolysis during autoclave sterilization
- **Cyclic olefin copolymer (COC)** – copolymer of norbornene and ethylene – good oxygen permeability (~ 1.2) and a low level of water permeability (~ 10) – both comparable to cyclic olefin polymer – difference is that that COC is brittle (elongation-at-break ~ 2%), and not suitable for multiple sterilizations
- **Note:** high-density polyethylene is not transparent – polypropylene is only translucent (e.g., Corning cryogenic vials)

V. Conclusion

For storage/delivery of parenteral drug products, polymers have many advantages over glass. Among polymers, cyclic olefin polymer (COP) (Daikyo Crystal Zenith® product) is the best choice.
VI. References

4. FDA Recalls, Market Withdrawals, & Safety Alerts

West’s products are sold on the basis that it is the customer’s responsibility to evaluate and test the West product to determine its compatibility with other materials and fitness for any end use.

This Technical Report dated 22 May 2017, is the first release version of this report.

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