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ADDRESSING THE CONCERNS OF GLASS USAGE FOR PREFILLED DRUG DELIVERY DEVICES: INTRODUCING A NOVEL CLASS OF ENGINEERED POLYMER

In this article, Satoru Adachi, Researcher, Product Development Team, Specialty Plastics Lab, and Mark Nevitt, Market Development Specialist, New Business Division, both of ZEON, highlight some of the concerns of using conventional glass for parenteral drug storage in prefilled syringes, and provide an update on ZEONEX® cyclo-olefin polymer (COP), a novel class of transparent plastic, and describe how COP can provide solutions to some of the issues persistently encountered when using glass in prefilled drug delivery systems.

As technological advances are made at an astounding rate in the drug discovery world, new and breakthrough drug therapies using protein-based pharmaceuticals are more rapidly becoming available to the general population for treatment of genetic and infectious diseases. In fact, protein-based pharmaceuticals have been identified as one of the fastest-growing classes of biopharmaceutical drugs in recent years,[1] being used in the treatment of such common diseases as diabetes, breast cancer and arthritis.[2]

> "Not only can leachables pose a serious health risk to the patient directly, but they can also potentially cause a health risk indirectly by rendering the drug dosage less effective by initiating protein agglomeration and/or the reduction of drug shelf life. Unlike glass, ZEONEX COP has been engineered specifically as an ultra-high-purity polymer with extremely low off-gas and leachable content."

While development and administration of protein- and peptide-based drugs is on the rise, there are ongoing discussions relating to the best storage and delivery systems for these often high-cost and environmentally sensitive biologics. Although the industry standard for drug storage and delivery has traditionally been glass vials and syringes, the steady increase in the number of patients who self-administer those drugs have caused the pharmaceutical industry to consider alternatives to traditional delivery methods, such as prefilled delivery systems, in an attempt to curb the risks of dosing errors and drug contamination.

In response, the prefillable syringe (PFS) is becoming one of the fastest-growing technologies in the injectable drug delivery market.[3] In the realm of PFSs, use of glass for syringes is the gold standard, for obvious reasons: a long history of use, high barrier properties and high transparency.

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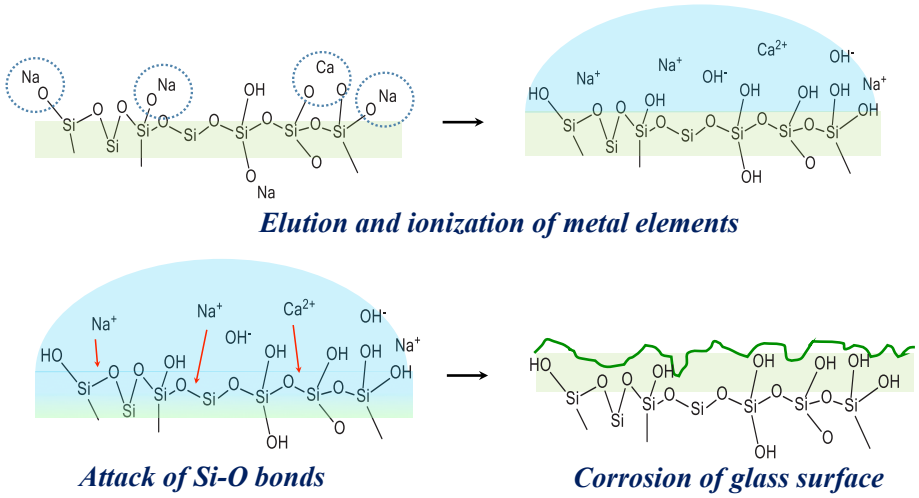


Figure 1: Mechanism of glass delamination.[6]

But as drug stability, purity and patient safety increasingly become a factor in the decision for best drug packaging and delivery solutions, syringes made of glass can potentially pose risk to the patient or compromise the high-value drug stored in the device. The solution is a novel class of engineered plastic – COP – that enables drug delivery system manufacturers to design a PFS that affords design freedom not previously obtainable with glass while promoting drug stability and patient safety on multiple levels.

Although it has been in commercial production for nearly three decades, ZEONEX COP remains a relative newcomer in the plastics industry compared with other olefins, polyamides (nylons), polystyrene and polycarbonate. However, the unique chemistry and physical properties of ZEONEX are being recognised and accepted by pharmaceutical companies as a preferable replacement to glass for a range of high-performance parenteral pre-filled drug delivery systems. The discussion that follows will serve to provide an understanding of the benefits offered by COP relative to glass.

> "When testing of ZEONEX COP resin was expanded to include a wider range of impurities, it was determined that no metals, solvents or low-molecular-weight components were detected in the stored solution. It is also notable that certain grades of ZEONEX COP have been tested to meet the requirements of USP <87> and <88> Class VI Biological Reactivity Tests."

PATIENT SAFETY, FIRST

According to the US FDA, "The administration of glass particulate, if present in a parenteral drug, can lead to sequelae of thromboembolism, some life-threatening (such as pulmonary emboli); phlebitis, mechanical block of the capillaries or arterioles; activation of platelets; and subsequent generation of microthrombi… Administration of a glass particulate can also lead to formation of granulomas, a protective local inflammatory response to the foreign material."[4]

While the cases have thus far been rare, there is increasing concern about glass and other micro-particles found in drug storage and delivery devices made of glass. In just the past few years, there have been multiple reports of product recalls by FDA relating to glass particulate caused by delamination of the glass storage devices' walls. In 2011, the recurrence of such reports prompted the FDA to issue an advisory statement to pharmaceutical companies pertaining directly to glass delamination. Some root causes were identified to be the processing method used in manufacturing the glass device, reagent pH and sterilisation methods.[5]

Taking a closer look at the mechanism that causes glass delamination, we find that metal elements are first eluted from the glass surface under certain conditions. Then, after ionisation, metal ions degrade the Si-O bond, causing erosion on the glass surface, as illustrated in Figure 1. The erosion can eventually lead to glass fragmenting and delamination (flaking). It is also important to pay attention to the first step of this process: metal elements are eluted from the glass surface. We will revisit that point later in the article.

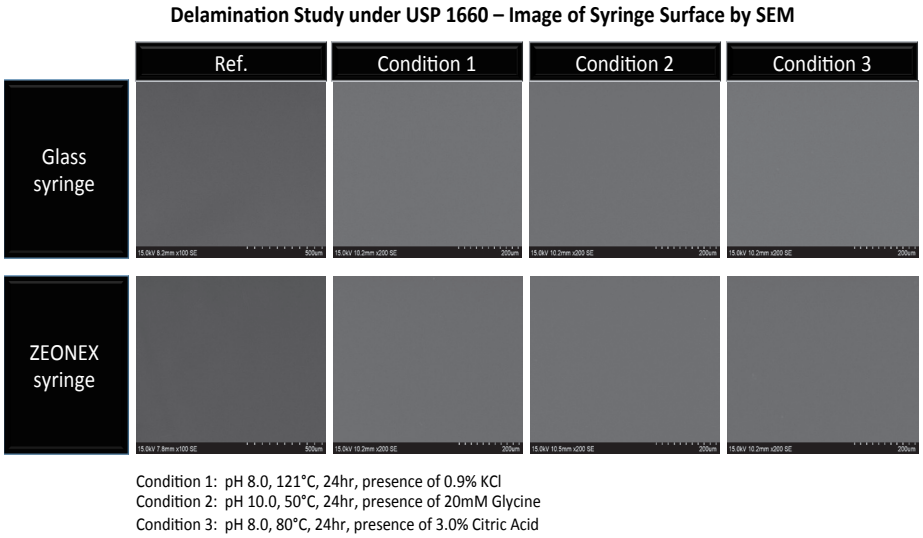
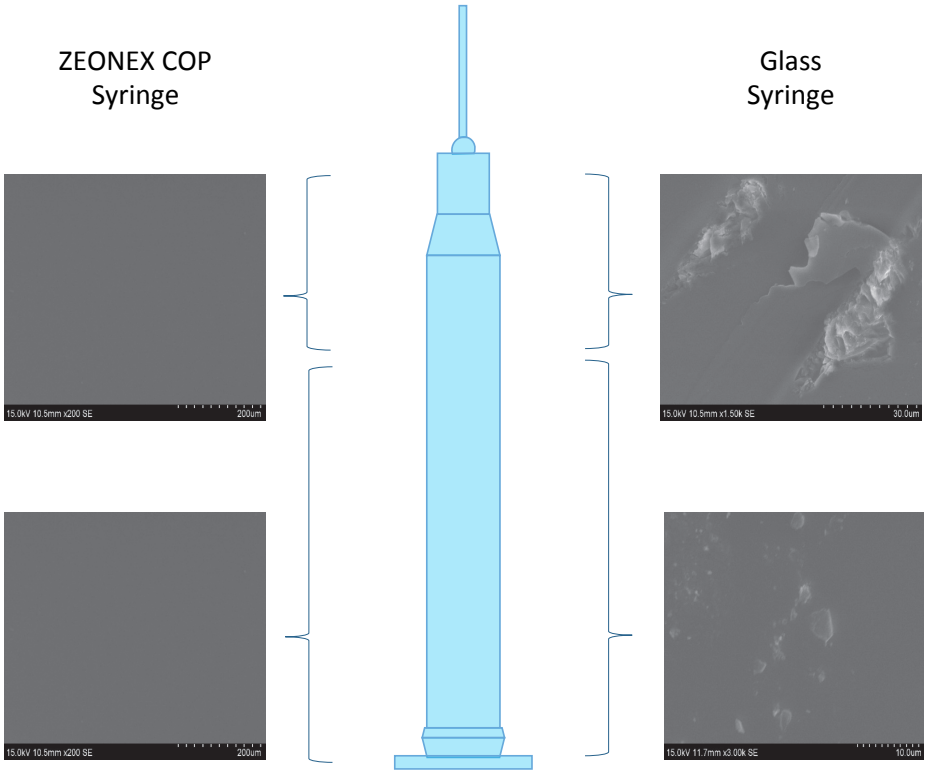


Figure 2: Result of delamination study under USP <1660>.

Zeon Corporation performed a study comparing the difference in particulate generation between syringes made of borosilicate glass – common in the manufacture of glass vials and syringes – and ZEONEX COP. The ZEONEX COP syringe was produced by conventional thermoplastic injection moulding practices, which provide for very high consistency of part dimensional and surface smoothness replication.

The test was conducted under the guidelines of United States Pharmacopeia (USP) Standard <1660> "Evaluation of the Inner Surface Durability of Glass Containers", which subsequently was created "in response to the recent product recalls that have further increased the pharmaceutical industry's heightened awareness of glass quality and glass delamination (i.e., the formation of glass flakes in a vial)".[7]



Storage condition:
pH 10.0, 80°C, 28 days, presence of 3.0% citric acid

Figure 3: Image of COP and glass syringe surface.

When storage conditions were set using the prescribed standard of 80°C at pH 8.0 for 24 hours in a 3% citric acid solution, no delamination was observed for either glass or the COP syringe (Figure 2).

However, when the same test was conducted under higher pH (pH 10.0) and extended storage conditions (28 days), the formation of microparticles was observed in the glass syringe, and was later verified as glass particulate by analytical measurement. It is interesting to note that more severe delamination was observed at the syringe tip compared with the barrel, where it is expected that the glass may have experienced a higher heat history during the manufacturing process (Figure 3). No delamination was detected in the ZEONEX COP syringe.

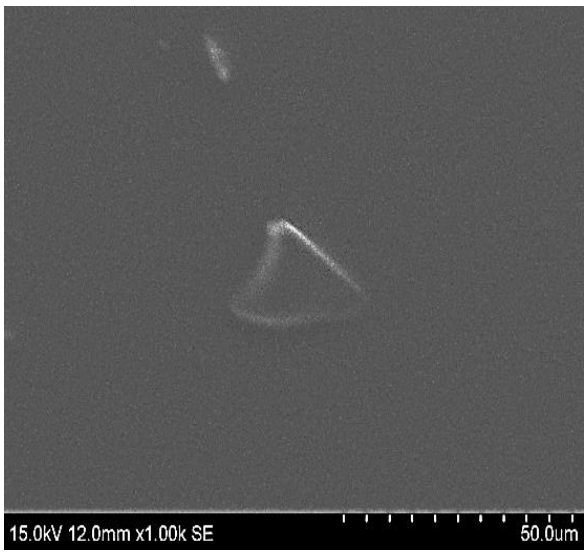
To establish additional confirmation of the delamination results, a third test was performed that more closely resembled a real-life storage scenario. That test incorporated a lower temperature (40°C), longer storage time (six months) and a pH of 8.0. Once again, glass particles were observed in the glass syringe (Figure 4), while no particulates were detected in the COP syringe.

LEACHABLE CONTENT, A SIGNIFICANT CONCERN

Earlier in this article it was discussed that the first step of glass delamination is elution of metal elements. As such, it is not surprising that leachables from the drug storage device are also a major concern to pharmaceutical companies in the long-term storage of their products. Not only can leachables pose a serious health risk to the patient directly, but they can also potentially cause a health risk indirectly by rendering the drug dosage less effective by initiating protein agglomeration and/or the reduction of drug shelf life. Unlike glass, ZEONEX COP has been engineered specifically as an ultra-high-purity polymer with extremely low off-gas and leachable content.

In a side-by-side test, glass syringes and ZEONEX COP syringes were filled with purified water and controlled at a pH of 7.0 and temperatures of 23°C and 40°C. After seven days, the water from each syringe was analysed by ICP-MS. As expected, a significant amount of tungsten was observed from the glass syringe while no tungsten was detected from the COP syringe. The tungsten found in the glass syringe is believed to have been transferred from the tungsten

Image of Glass Particulate at 'mild' condition



Storage condition:
pH 8.0, 40°C, 6 months, presence of citric acid

Figure 4: Image of glass particulate.

Result of Tungsten Elution Test by ICP-MS

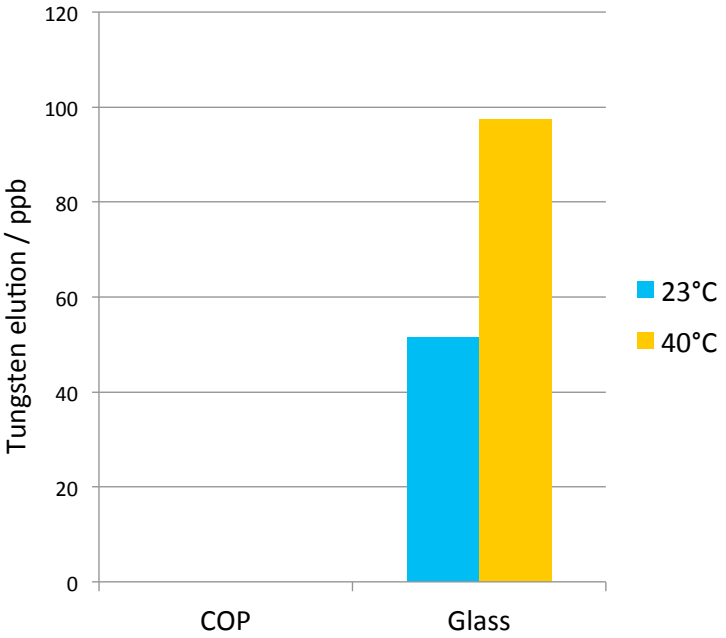


Figure 5: Measurement of tungsten concentration in water after storage in COP and glass syringe.

pin commonly used in the glass moulding process.

Although this particular study was isolated to tungsten contamination, it is well known and documented that silicon, sodium and boron are the most problematic leachables from glass. Potassium, barium, calcium and aluminium also have potential to contribute to the contamination of stored drugs.[8] Comparably, when testing of ZEONEX COP resin was expanded to include a wider range of impurities, it was determined that no metals, solvents or low-molecular-weight components were detected in the stored solution. It is also notable that certain grades of ZEONEX COP have been tested to meet the requirements of USP <87> and <88> Class VI Biological Reactivity Tests.

PROTEIN ADSORPTION, A STICKY ISSUE

We have discussed two ways in which contaminants can originate from glass (particulates and eluents). Glass can also contribute to a decrease in drug efficacy by the drug proteins migrating to the glass, commonly referred to as adsorption. Proteins exhibit a certain degree of surface activity, and tend to adsorb to glass, rubber and plastic due to their amphiphilic polyelectrolytic nature. Several factors can contribute to the amount of protein adsorption that occurs. However, the result of adsorption is always a reduction in the biological activity of the drug.[8]

While it is well documented that protein adsorption is an ongoing concern for storage of protein-based drugs in glass and conventional plastics, the unique amorphous, fully saturated chemical structure of ZEONEX COP offers a significant performance advantage over other materials by inhibiting adsorption of most proteins. To confirm that, a study was performed in which bovine serum albumin (BSA) was stored in a borosilicate glass syringe and a ZEONEX COP syringe, then measured weekly by high-performance liquid chromatography (HPLC) to determine the adsorption rate of the protein to the surface of each syringe. As illustrated in Figure 6, it is evident that COP demonstrates a very low rate of adsorption while glass exhibits a steady increase of adsorption over the same period. Testing has also been performed at varying pH levels (results not shown here) wherein COP continues to demonstrate excellent inertness to protein adsorption.

In addition to adsorption, protein aggregation (the agglomeration of the protein molecules) is also a mechanism by which drug efficacy can be diminished. One of the catalysts for protein aggregation is the presence of silicone oil, which is used to improve the sliding friction of the plunger in both glass and plastic syringes (including COP). Silicone oil can also migrate from the syringe surface, causing undesirable microparticles in the drug suspension that can be injected into the body along with the drug.

As ZEONEX COP gains recognition for its benefits in long-term parenteral drug storage, a number of drug delivery device makers have recently developed silicone oil-free syringes based specifically on COP substrate. It is expected that the new technology of silicone oil-free systems, coupled with the inherent inert nature of COP, will further contribute to the improvement of drug stability and quality afforded by ZEONEX COP over glass syringes.

ZEONEX COP, ADDRESSING THE CONCERNS OF GLASS USAGE FOR PFSS

While glass is expected to maintain a dominant position for use in PFSs due to its exceptional gas barrier properties, there will continue to be prefilled drug delivery systems for which the concern for leaching, delamination and protein adsorption must be addressed. ZEONEX COP, with its inherent qualities of high transparency, high moisture barrier, high purity, inertness, break-resistance and precision mouldability is capable of providing a superior solution that addresses the concerns of glass usage.

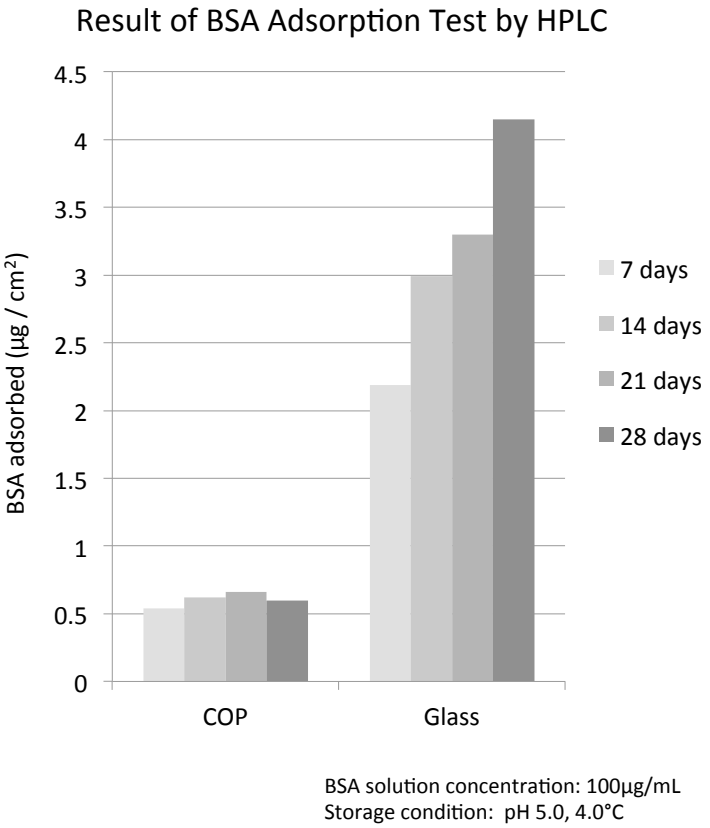


Figure 6: Result of BSA adsorption test.

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