POLYMER SYRINGE CONSIDERATIONS FOR DRUG APPLICATIONS AND ADMINISTRATION

In this article, Tibor Hlobik, Senior Director, Product Management, West Pharmaceutical Services, compares cyclo-olefin polymers and copolymers with glass as the material of choice for prefilled syringes, in particular discussing the benefits of polymers when it comes to biologic drug products and prefilled syringes for use in autoinjectors.

BACKGROUND

Manual prefilled syringes offer a number of benefits, including cost advantages, simpler manufacturing processes and ease of administration. However, there are several limitations, including dosing/medication errors if not used as prescribed and the potential for needlestick injuries resulting in a safety risk. Patient adherence and outcomes may be improved with the addition of an autoinjector to the syringe that is relatively easier to use, has integrated needle safety features and allows for self-administration that decreases the need for visiting a healthcare centre for treatment. Autoinjectors are also considered a valuable lifecycle management approach, used by many pharmaceutical players to expand marketing exclusivity periods of proprietary drugs.

The demand for prefilled syringe-based autoinjectors continues to be strong. Historically, these were widely used as an emergency treatment option for anaphylaxis and autoimmune treatments. Now they are being applied in multiple treatments for chronic diseases that require frequent injections, such as diabetes, rheumatoid arthritis, psoriasis and multiple sclerosis. The strong pipeline of biologics is further driving the growth of autoinjectors.

Glass prefilled syringes have traditionally been the standard in autoinjector applications. Recently, cyclo-olefin syringes are being combined with autoinjectors for complex drug delivery applications, with several drugs on the market already approved by regulatory agencies. This combination can bring differentiated value to the patient. One publicly announced example[1] is Ypsomed's (Bergdorf, Switzerland) YpsoMate® with a Terumo (Tokyo, Japan) PLAJEX™ syringe for the drug Hulio® (adalimumab); a biosimilar to Humira® (AbbVie, Lake Bluff, IL, US) developed by Fujifilm Kyowa Kirin Biologics (Tokyo, Japan) and marketed in the EU by Mylan (Canonsburg, PA, US).

CYCLO-OLEFIN POLYMER – MATERIAL REVIEW

There are two primary types of engineered polymers used to manufacture prefillable syringes: cyclo-olefin copolymer (COC) and cyclo-olefin polymer (COP). To date, COP syringes have been a primary choice for biologic drug applications. A chemistry overview of each material type is provided for reference.

COP is made by ring-opening metathesis polymerisation of norbornene (or a derivative) with Grubbs catalyst (e.g. $Ru[P_2C_3H_2(C_6H_5)_8]Cl_2$), followed by solution-phase hydrogenation with a diimide compound (Figure 1). Diimides, such as 4-methylbenzenesulfonhydrazide, are well known compounds for hydrogenating double bonds. From a commercial standpoint, they offer the great advantage of

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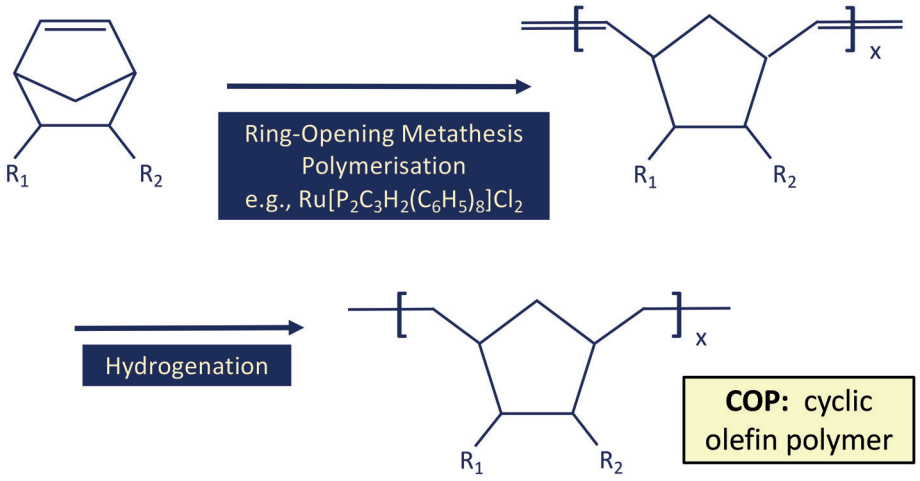

Figure 1: Structure and synthesis of a COP. Poly(norbornene) is represented where R1 and R2 are hydrogen.

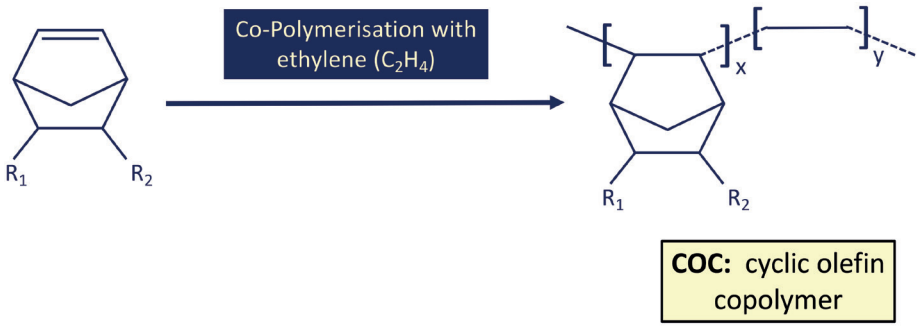

Figure 2: Structure and synthesis of a COP. Poly(norbornene-co-ethene) is represented where R1 and R2 are hydrogen.

avoiding the need to use gaseous hydrogen. By-products of the reaction are nitrogen gas and compounds that can be removed easily by washing. The molecular weight (Mw) of COP is typically ~ 7 x 104, with a polydispersity of ~ 2.

In contrast, COC is made by metallocene-catalysed (e.g. $Ti[(C_5H_5)_2]Cl_2$) co-polymerisation of norbornene (or derivative) with ethene (Figure 2). While this has some advantages, there are likewise drawbacks. Advantages are employment of a low-cost monomer (ethene) and no need to hydrogenate after polymerisation (one step versus two steps). Both points offer a cost advantage. However, a typical commercial product that has a glass transition temperature (Tg) that can withstand autoclave sterilisation (steam at greater than 120 °C) will have a high norbornene content (offsetting the ethene cost benefit) and is brittle.

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	Glass (Mw %)	Polymer (Mw %)
SiO_2	70–82	–
B_2O_3	5–13	–
Al_2O_3	2–7	–
CaO/MgO/BaO	0–7	–
Na_2O/K_2O	4–12	–
C	–	85
H	–	15
Catalyst	–	trace

Table 1: Chemical composition of typical tubular Type I borosilicate glasses and typical polymer (polyethylene).

Chemistry Comparison

Glass used for pharmaceutical primary containers is typically Type I borosilicate (according to the United States Pharmacopoeia and European Pharmacopoeia). The compositions of Type I glass and an analogue polymer for COP (e.g. polyethylene, $[C_2H_4]_x$), are given in Table 1. Glass comprises at least five oxides, the cations of which can leach into a drug product. According to ICH Q3D (Guideline for Elemental Impurities) for new finished drug products, a strategy to limit elemental impurities must be developed. The table of impurities listed in ICH Q3D cites several ions that are present in glass.

Certain proteins or drug products, due to the buffer or excipient, are sensitive to certain elements that can leach from glass, such as aluminium, barium or calcium. In contrast, polymers such as polyethylene comprise essentially only carbon and hydrogen (constituents of all drug products) and thus, intrinsically, the risk of a leachate causing an issue is reduced substantially.

Surface Interaction and Silicone Oil Risk

Glass has a high surface energy, while lower energy materials (e.g. butyl rubber) tend to adhere. Practically, this means that an elastomer plunger made of butyl rubber will tend to adhere to the inside wall of a 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 and facilitates easier movement of the plunger, which is a desirable feature.

As noted prior, the inner surface of a glass syringe must be siliconised (i.e. have a thin coating of silicone oil applied, typically sprayed, with sometimes resultant coating being baked) in order to provide lubricity to enable effective plunger movement. This is necessary because the lower surface-energy elastomer stopper will tend to adhere to the higher surface-energy glass surface. However, there are two issues with the presence of silicone oil:

- **Particles:** The presence of silicone oil intrinsically creates the risk of introducing visible and sub-visible particles into the drug product – particles that will be injected into the patient. This is clearly a risk to patient safety.
- **Protein Aggregation:** Proteins can aggregate to form particles in the presence of silicone oil and the drug efficacy can be compromised.

It is well known that silicone oil can cause alteration/denaturation of protein molecules, resulting in the formation of particulates which are unacceptable, as particulates can result in diminished/deleterious effects. A substantial amount of literature addresses the issue of protein aggregation and resultant particle formation.[2-7] In syringes comprising lower surface energy polymers, siliconisation is not needed. Thus, a lower-risk solution is to employ a COP-based syringe, which has a lower surface energy and thus enables plunger movement without the need for silicone oil.

Physical Properties – Modulus/Strength/Brittleness

Glass Type I borosilicate has a very high modulus of elasticity (Young's modulus), and thus stiffness (Table 2). This manifests as a high brittleness compared with many polymer materials, which instead show high ductility. The energy that is introduced from a strong impact cannot be absorbed by glass, but instead causes it to fracture. Due to its amorphous nature, glass strength is not a material constant, but rather depends on the intactness of the surface. This intactness is strongly influenced by manufacturing and processing, starting with tubing production, through the converting process and filling line, up to point of administration.

Glass has an impact resistance of only ~20 J – as compared with ~ 550 J for a polymer (Table 2). This means that the chances of glass breakage are substantially higher. In syringes, this has been demonstrated experimentally. Flange strength of syringes comprising glass was compared with those comprising a poly(norbornene)-based COP polymer (Table 3). This may appear counterintuitive, that a polymer requires more force to break even though glass has a higher tensile strength. The reason is this: a polymer can undergo deformation under stress, whereas glass cannot, and thus a polymer can accommodate a higher force prior to fracture. This is reflected by the higher impact strength of polymers. The net result is that a polymer syringe provides a much more durable product (i.e. less likely to fracture) in an autoinjector.

Property	Glass	Polymer
Elastic Modulus – GPa	~ 70	0.8 (a)
Tensile Strength – MPa	70–100	15 (a)
Impact Strength – J (c)	~ 20	~ 550 (b)

Table 2: Mechanical properties of glass versus polymers (a: Polyethylene, b: Poly(norbornene) – Daikyo Crystal Zenith® cyclo-olefin polymer, c: Tested with a Dupont (Wilmington, DE, US) impact tester).

Material	Force to Break (N)
Glass	~ 250
Daikyo Crystal Zenith® cyclo-olefin polymer	>500

Table 3: Syringe flange strength.

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Protein Adsorption Consideration

In addition to having a higher surface energy than a polymer, and therefore being more likely to interact with a protein molecule (promoting the issues just noted), glass carries a net negative charge, resultant from SiOH groups.

This enables an electrostatic interaction between glass and protein. A polymer surface, in contrast, has only a marginal charge, due to the general absence of ionisable groups (except a possible small amount of alcohol (R-OH) or carboxylic acid (R-COOH) groups). Interactions between polymer and protein, therefore, would be governed not by stronger electrostatic effects, as is the case with glass, but by much weaker dispersion forces. What is expected, based on theoretical considerations, has been demonstrated experimentally – proteins interact much more strongly with glass than polymer. Several studies have compared the adsorption of proteins with vials comprising glass and polymer.[8,9]

The adsorption of proteins to the surfaces of container systems is an issue for two reasons:

- **Concentration:** For drug products formulated at a high concentration of API, such as monoclonal antibodies, the amount adsorbed is likely insignificant. However, where the drug product is formulated at a low API concentration (e.g. tens of µg/mL), the amount adsorbed can represent a significant fraction. As a consequence, the manufacturer may need to formulate at a higher API concentration than medicinally necessary, resulting in higher cost for the patient.
- **Performance:** Of more concern, protein adsorbed to a surface can serve as a nucleation site leading to the formation of protein particles. It has been demonstrated by Philo and Awakara[10] that proteins can aggregate by five different methods. These particles may become dislodged (e.g. due to mechanical stress such as agitation), potentially leading to the formation of larger aggregates. This has been demonstrated by Gerhardt *et al.*[4] Furthermore, a growing body of evidence suggests that protein aggregates can be immunogenic, for example as reported by Rosenberg.[11] This is an extremely serious issue.

Proteins interact much more strongly with glass than polymer, which leads to issues of diminished API concentration in drug product and, worse, formation of particles that may be immunogenic. Clearly, with a biologic drug product, the lower risk option is a cyclo-olefin polymer.

CONCLUSION

Greater scrutiny must be paid to the interaction between the drug and prefillable syringes. Drug stability over the shelf life, particulate burden, the prevention of

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breakage (e.g. body and flange) and ease of delivery are some important factors to consider. In addition, regulatory agencies and pharmaceutical companies have increased their quality expectations in an effort to enhance patient safety.

High-quality cyclo-olefin polymer prefillable syringes are a proven solution and have differentiated benefits over glass in areas of chemistry, physical properties and protein adsorption. Engineered polymer syringes present attractive benefits that are gaining increased attention from drug manufacturers seeking new answers to growing drug challenges.

ABOUT THE COMPANY

West Pharmaceutical Services is a manufacturer of packaging components and delivery systems for injectable drugs and healthcare products. Working by the side of the world's leading pharmaceutical, biotechnology, generic drug and medical device producers from concept to patient, West creates products that promote the efficiency, reliability and safety of the global pharmaceutical drug supply. Additionally, West provides a comprehensive Integrated Solutions programme that combines high-quality packaging and delivery systems with analytical testing, device manufacturing and assembly, and regulatory services to support customers throughout the drug development lifecycle.

West is headquartered in Exton, PA, US, and supports its customers from locations in North and South America, Europe, Asia and Australia. West's 2019 net sales of US$1.8 billion reflect the daily use of approximately 112 million of its components and devices, which are designed to improve the delivery of healthcare to patients around the world.

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REFERENCES

1. *"First market entry of YpsoMate autoinjector from Ypsomed". Press Release, Ypsomed, December 7, 2018.*
2. *Jones LS, Kaufmann A, Middaugh CR, "Silicone oil induced aggregation of proteins". J Pharm Sci, 2005, Vol 94(4), pp 918–927.*
3. *Thirumangalathu R et al, "Silicone oil- and agitation-induced aggregation of a monoclonal antibody in aqueous solution". J Pharm Sci, 2009, Vol 98(9), pp 3167 –3181.*
4. *Gerhardt A et al, "Protein Aggregation and Particle Formation in Prefilled Glass Syringes". J Pharm Sci, 2014, Vol 103(6), pp 1601–1612.*
5. *Chisholm CF et al, "In Vivo Analysis of the Potency of Silicone Oil Microdroplets as Immunological Adjuvants in Protein Formulations". J Pharm Sci, 2015, Vol 104(11), pp 3681–3690.*
6. *Krayukhina E et al, "Effects of Syringe Material and Silicone Oil Lubrication on the Stability of Pharmaceutical Proteins". J Pharm Sci, 2015, Vol 104(2), pp 527–535.*
7. *Waxman L, Vilivalam V, "Evaluation of End-Over-End Rotation/Agitation of Protein Solutions in Prefilled Syringes Made from Glass or Plastic as a Preliminary Indicator of Protein Aggregation". Technical Bulletin, West Pharmaceutical Services, 2011.*
8. *Qadry SS et al, "Evaluation of CZ-resin vials for packaging protein-based parenteral formulations". Int J Pharm, 2003, Vol 252(1–2), pp 207–212.*
9. *Eu B et al, "Direct visualization of protein adsorption to primary containers by gold nanoparticles". J Pharm Sci, 2011, Vol 100(5), pp 1663–1670.*
10. *Philo JS, Arakawa T, "Mechanisms of Protein Aggregation". Curr Pharm Biotechnol 2009, Vol 10(4), pp 348–351.*
11. *Rosenberg AS, "Effects of protein aggregates: an immunologic perspective". AAPS J, 2006, Vol 8(3), pp E501–E507.*

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