PART I OF II: IMPROVED PARENTERAL CONTAINERS THROUGH PLASMA DEPOSITION OF HIGH PURITY GLASS

In this piece, the first of a two-part article, Kevin Turney, Senior Applications Development Scientist, and Peter Sagona, Vice-President and Secretary, both of SiO2 Medical Products, and Shawn Kinney, consultant to SiO2 Medical Products, describe the company’s plasma coating technology that allows a nanometres thin layer of glass (in fact, pure silicon oxide) to coat plastic (cyclic olefin polymer) parenteral drug containers and delivery systems, thus imparting the barrier properties and other advantages of glass with the benefits of polymer devices within the same device. We’re pleased to confirm that part two will appear in the February 2014 issue of ONdrugDelivery Magazine.

INTRODUCTION

SiO2 Medical Products (SiO) is a vertically integrated manufacturer of high-quality, high-volume pharmaceutical and medical device components formed to develop and commercialise precision-moulded plastic products lined with thin, transparent silicon-oxide based coatings. The coating layers are applied using plasma enhanced chemical vapour deposition (PECVD). A precision polymer container with a technically advanced coating system creating an inert, glass-like product contact surface, is ideally suited for packaging of injectable biopharmaceuticals and high purity drug compounds. Together, this allows SiO to offer primary parenteral containers with superior performance when compared with current glass or plastic containers.

BACKGROUND ON EXISTING CONTAINERS

For decades, glass has been the most commonly used material for manufacturing parenteral containers. Glass is readily available, strong, mouldable to typical container shapes and sizes, easy to clean and sterilise, and relatively inert. Despite these positive attributes, glass has shortcomings that make it a less than ideal material of construction for parenteral containers.

Borosilicate glass is not pure silicon dioxide. Glass manufacturers incorporate inorganic additives into the base raw materials to improve...
handling and manufacturability of molten glass; these additives include oxides of boron, calcium, sodium, and aluminium. Fundamentally, the raw material used to manufacture glass is still naturally derived; the raw sand contains low levels of impurities, including iron, that vary with the location of the source. Raw material control is variable and has the potential to impact extractables, and the integrity of the container.

Glass delamination is an important topic in current pharmaceutical trade literature leading to the drafting of a USP general information chapter, USP 1660. Under specific conditions, glass particles may flake off from the inner surface of parenteral containers due to delamination mechanisms, many of which relate to inorganic additives within the glass formulation. Delamination has been suggested as the root cause for US FDA product recalls due to glass particulates (i.e. lamellae).  

Glass products are prone to breakage, which can occur upon receipt of the incoming container, filling of the product on manufacturing lines, transport, usage within auto-injector assemblies, and during administration. Each instance of breakage of a parenteral package causes a cascading effect, as it results in potential contamination of other containers and equipment, possible breach of sterility, as recalls of the product due to visible particulates, and safety risks. Within the manufacturing environment glass bruising, caused by vial to vial contact, introduces flaws and stresses which later can result in cracking and breakage following small stresses to the container. In essence, when a glass container is dropped or exposed to certain mechanical stresses, it should be discarded from risk mitigation alone. Combination products, such as auto-injectors, pose an added concern when glass containers may not be visible to examine breakage.

In traditional moulding methods, glass containers are produced with large dimensional variance. These deviations can cause issues in auto-injectors and speciality delivery devices that require very tight and reproducible dimensions. Failure to maintain specific tolerances can lead to non-obvious failures or jams of devices and auto-injectors, potentially underdosing an unknowing patient. Glass is limited in its ability to be moulded into non-standard shapes and sizes limiting the use of glass in future applications.

An additional contaminant in borosilicate glass syringes, tungsten, was found to cause precipitation and aggregations in some protein-based products. The source of the tungsten was traced to the forming pins which are used to form the lumen of the tip. Tungsten deposited in the lumen as tungsten oxide interacted with some protein formulations leading to precipitation.

**PLASMA DEPOSITION TECHNOLOGY**

A new paradigm in materials of construction for parenteral containers has emerged from SiO: plastic containers made of medical grade polymers (cyclic olefins) coated and incorporating a very thin, transparent layer of pure silicon oxide. Pure silicon oxide lacks metal oxide additives implicated in glass delamination; it also blocks extractables/leachables, oxygen and even label adhesive from migrating into the drug product. Plastic containers coated with silicon oxide, promise to be the ideal materials of construction for parenteral containers. The ultrathin silicon oxide is flexible, and not prone to breakage or delamination under mechanical or thermal stresses.

An innovative plasma deposition process has been developed (see Figure 1) that deposits a pure, ultrathin layer of silicon oxide on plastic containers. This process creates parenteral storage containers that have all of the advantages of both glass and plastic without many of the shortcomings of either.

Plasma deposition of glass is not new; it has been used for many years to coat items from bottles to computer chips to artificial lenses. What is novel is the plasma process, the thinness of the coating, a discrete coating to provide a broad range of pH stability in parenteral products, and the use of individual containers as the vacuum chamber for the plasma. By depositing the coating via individual containers versus batch processing the system is scalable for production and offers a consistent and uniform coating of the containers, delivering consistent performance.

The plasma process utilises pure organosiloxane monomers and gases. The container to be coated is sealed in a puck that provides an electrode and a gas inlet (see Figure 1). A vacuum is applied to the container through the puck and then the process reactants (e.g. hexamethyl-disiloxane (HMDSO), argon, and oxygen) are introduced through the gas inlet tube. Once a steady state is achieved, the gaseous mixture is then excited by radio frequency (RF) energy to establish a plasma inside the container. The plasma deposits a uniform silicon oxide coating layer on the inside surface. By controlling pro-
cess parameters the chemistry, uniformity and deposition rate allow for consistent thickness and barrier properties. Spectroscopic process analytics have been established to monitor the plasma for each unit produced.

This coating process produces a container with an ultrathin layer of pure silicon oxide that is just nanometres thick. Thickness is very important because thin layers of glass are flexible and consequently give under strain rather than resist and break as do thick layers of glass. We have shown that these plasma-coated polymer surfaces can withstand a deflection, which would cause a glass container to shatter, with no loss of coating adhesion. In fact, we have found that the glass coating integrity and adhesion is maintained even to the point that the plastic itself is permanently deformed.

BARRIER COATING SYSTEM

After deposition of the thin silicon oxide coating layer, other plasma coating layers can be applied. Changes to the plasma processing conditions, including changes to the gases and monomers, allow the customisation of coatings. An example of a barrier coating system is the addition of a top coat over the silicon oxide coating providing protection from hydrolytic attack. In SiO2 Medical Products’ barrier coating system, each coating layer is applied in a separate PECVD process. First a silicon oxide layer is applied to the container. After the silicon oxide layer is applied, the container is transferred to a second coater where the top (pH protective) layer is applied. Alternative processes can be employed to tailor hydrophobicity. The coatings can be customised dependent upon the contact surface needs, as shown in Figure 2.

An example barrier coating system (a barrier layer and top hydrolytic attack protection layer) for a staked needle syringe is shown in Figure 3. Transmission electron microscopy (TEM) is used to image the coatings inside the syringe barrel. This coating system was developed to provide a barrier to high pH injectable formulations. Glass dissolves in water at high pH. With a borosilicate glass container a few microns of the glass surface are dissolved. Under no circumstance would the entire glass container be dissolved, due to saturation of the solution, yet contaminants, silicon and other metals within the glass do migrate into the drug formulation. Being only nanometres thick, the silicon oxide coating, which provides the barrier properties to oxygen and potential leachables, must be protected from hydrolytic attack. Protection is provided by the top layer coating system. In Figure 3, from left to right in the TEM one can see the protective layer, the silicon oxide barrier layer and polymer.
container surface. The elemental composition of each coating is shown in the XPS (x-ray photoelectron spectroscopic) within Figure 4. The top layer has a composition of silicon, oxygen, and carbon in a ratio of 1:1:1. The barrier coating has a composition of silicon and oxygen in a ratio of 1:2. Each layer’s composition is uniform throughout until the discrete transition to the next layer on the container surface. By XPS and other techniques, each layer has been shown to be bonded to the underlying layer.

We have demonstrated that the silicon dissolution rate of our coating system is approximately 100-fold less than that of standard borosilicate glass. Long-term stability studies with solutions ranging in pH from 3.5-8, with surfactants, a variety of different buffer types and ranges of salt concentrations have shown years of shelf life, determined by maintenance of the barrier layer’s barrier performance.

CONCLUSION

The innovative material described here is a combination of plastic with a pure glass barrier coating system to produce a new parenteral container material that has optimal properties for clarity, pH stability, resistance to breakage, dimensional tolerances, improved barrier properties to gas and solutes, and increased purity. This blend of plastic and glass creates the ideal parenteral container material for drugs and biologics.

This article has focused on the details and explanation of our barrier coating system describing the plasma process, composition of the resulting coatings and purpose of the layers that comprise the coating system. We have discussed the benefits of this barrier coating system over glass and plastic from a purity, barrier and breakage perspective. The second part of this article, which will appear in the February 2014 issue of ONdrugDelivery Magazine, will describe the characterisation of the barrier coating system from a performance perspective with physical, chemical and thermal stresses that a parenteral storage container must be able to withstand. It will also feature additional detailed evidence of the benefits of our barrier coating system.

“THIS PROCESS CREATES PARENTERAL STORAGE CONTAINERS THAT HAVE ALL OF THE ADVANTAGES OF BOTH GLASS AND PLASTIC”

REFERENCES


ABOUT THE AUTHORS

Shawn Kinney:
A consultant to SiO2 Medical Products (SiO) on the parenteral drug market, Shawn Kinney, PhD, is the founder of Hyaluron, a contract manufacturer of injectable therapeutics. Dr Kinney has presented at many conferences and authored numerous articles relating to pre-filled syringes. He provides technical and marketing assistance to SiO regarding the design of parenteral containers, secondary packaging and coating stability. He holds a Doctorate in Chemistry from the University of Massachusetts at Amherst.

Peter Sagona:
SiO Vice-President and Secretary, Mr Sagona is responsible for programme management, including overall project coordination of deliverables and timelines. Mr Sagona also oversees the intellectual property strategy associated with the program. Prior to joining SiO, Mr Sagona spent 11 years with CV Holdings LLC, and seven years at SmithKline Beecham Clinical Laboratories managing automation development projects. Mr Sagona received an MS in Engineering Management from Drexel University.

Kevin Turney:
Senior Applications Development Scientist at SiO2 Medical Products, Dr Turney is responsible for technical evaluation and implementation of plasma coated parenteral containers. He coordinates customer development activities through internal and external scientific resources. Dr Turney has a PhD in Analytical Chemistry from the University of Florida. Prior to joining SiO2 Medical Products he was a Senior Scientist within R&D at Amgen, where he was Group Leader for Structure Elucidation.

ABOUT SiO2 MEDICAL PRODUCTS

SiO2 Medical Products (SiO) is a manufacturer of plastic primary containers, with a thin glass coating on the interior surface. SiO is a privately held company located in Auburn, Alabama USA. SiO was founded and is supported by CV Holdings, LLC, an organisation with 90 years of manufacturing experience, developing and manufacturing packaging for diagnostic applications, food and dairy worldwide. SiO’s R&D and manufacturing facilities are housed in a pilot facility in Auburn, with professionally staffed, fully equipped analytical and mechanical laboratories. SiO will move to its newly constructed 160,000 square foot headquarters nearby in first quarter 2014. The state-of-the-art facility contains three ISO Class 7 clean rooms, each spanning 10,500 square feet and dedicated to SiO’s glass coating and packaging lines. Plans are in place to build a second manufacturing plant in Strasbourg, France to provide duplicate manufacturing capabilities.

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