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CRITICAL MATERIAL CONSIDERATIONS FOR DRUG CONTAINMENT

Here, Dick Molin, Medical Market Segment Manager, Specialty Coating Systems, highlights some of the hazards that arise through the use of traditional lubricious coatings, such as silicone oil in syringes, pumps and other parenteral delivery devices. Particular focus is paid to the problems of protein aggregation and trace impurities leaching from elastomeric components before going on to describe how the polymer Parylene, applied as a very thin coating using the company's unique deposition method, avoids them.

THE GIVEN NEED FOR SAFETY

The safe and effective containment of pharmaceutical products is paramount to the successful treatment of patients. To that end, as new, aggressive drug chemistries and compounds are developed, choosing the right packaging material is becoming increasingly critical. Newer chemistries have been shown to affect the long-term reliability of some traditional materials, which necessitates a re-examination of the existing materials and strategies used to preserve the purity of medications, particularly those that are stored for an extended period.

For any given containment system (e.g. a vial, IV kit, prefilled syringe or insulin pump), the patient and administrator rely on the flawless performance of each and every material and component. As medications must remain pure, the materials themselves cannot act as a contaminant or as a catalyst for undesired effects. Since today's ever changing list of available pharmaceuticals includes medicines that can indeed be impacted by their containment systems, it is up to materials experts and device manufacturers to ensure the protection of medications. Of concern first and foremost is the preservation of purity, which is achieved through strict control of manufacturing, filling, packaging and storage processes.

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As previously stated, it is critical that medicine loaded into a containment system remains unaffected by any and all surfaces with which it comes into contact.

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One known possibility is the potential for trace contaminants in packaging materials to leach into the medicine, compromising its purity. For example, trace elements in one or more components of a given elastomer blend can be problematic, as can environmental contaminants that are unintentionally added during component manufacture or assembly. Even known materials that are added to enable specific performance characteristics – e.g. to provide lubricity to ensure smooth and reliable dosing – may be an issue. One or more of these concerns may be present and are particularly an issue for elastomeric components, which are vital for making seals, ensuring reliable containment and enabling complete and accurate delivery of the intended dose.

The preference, of course, would be to use a pure, fully compatible material to avoid such hazardous conditions. However, those options are scarce and do not always maintain one critical characteristic – lubricity. A variety of additive materials have been used over the years to improve lubricity on preferred materials, with the challenge being to achieve the desired balance between adequate barrier properties and the appropriate level of lubricity to ensure proper delivery mechanics.

In the examples of a prefilled syringe and an insulin infusion pump, the dosing mechanism may rely on the infrequent movement of a plunger within a reservoir. The use of traditional spray-type lubricants, such as silicone oil, may impart the required lubricity but provide no barrier properties to leachables. Additionally, the longer such spray-type lubricants sit unused, the less reliable they become due to their migration from critical contact surfaces. Silicone oil is also known to create longer-term storage issues related to particle and protein aggregate levels of some common solutions.

Among the more familiar and common protein drugs is insulin, which is typically delivered via standard syringe, pump or prefilled syringe. Prefilled syringe technology is particularly noteworthy as it continues to experience increased adoption throughout the industry. With an estimated three billion prefilled units manufactured in the year 2013, forecasts indicate production will grow to 6.7 billion by 2020. As can be attested to by regular insulin users, medication cloudiness is often observed after weeks or months in storage as a result of aggregation due to the influence of silicone oil droplets. While cloudiness has not been demonstrated to be enough to deem the dose entirely unusable, it has been determined to impact medicinal value – to the detriment of the patient and, consequently, the drug manufacturer. Studies have shown a direct cause and effect between cloudiness and low molecular weight silicone oils. As such, efforts are being made to reduce this effect by tailoring silicone oils, but successes achieved thus far have been limited.

While insulins are the most common medications affected by silicone oils, there are others with which similar issues have been discovered. Monoclonal antibodies (mAbs) are cited to be one example. Chemotherapy drugs are often joined to mAbs to create a targeting mechanism for specific types of cancer cells. Another drug subject in controlled aggregation studies is ranibizumab (Genentech's Lucentis®), an mAb fragment used to treat macular degeneration. These classes of drug, amongst others, stand to lose efficacy over time in storage due to the detrimental aggregation related to the use of silicone oils.

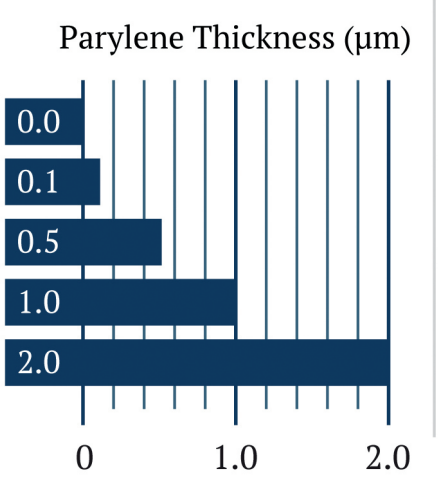
THE PARYLENE ANSWER

The challenge posed by the storage of these (and similar) compounds has been addressed by using a vapour-deposited polymer commonly known as Parylene. Parylene conformal coatings offer a pure, extremely thin, lubricious replacement to silicone oils. Typically applied in thicknesses of only 1-2 µm, Parylenes impart the required lubricity to minimise break-out forces while also providing barrier properties that can enhance long-term solution purity, which may otherwise be compromised by leachable substrate impurities (Figure 1). Also of great benefit is Parylene's benign chemistry, which does not result in the detrimental aggregation seen with silicone oils.

Parylene conformal coatings have a long history of protecting devices that span the entire medical device application range – from externally communicating to implantable. Included in the Parylene portfolio are life-saving and life-enhancing technologies such as cardiac pacemakers, neurostimulators, shunts, cochlear and retinal implants, and electrosurgical tools. Also included are infusion components like needles, barrels, plungers, seals and septa, as well as high-purity storage containers, protecting both the device from the drug and the drug from the device. Additionally, Parylenes are well suited for use on combination devices such as prefilled syringes and drug-eluting coronary stents.

Because Parylenes are applied under vacuum via a vapour deposition process, the size and complexity of components do not inhibit the coating's ability to form a conformal layer of protection. Coating with Parylene has virtually no impact on the dimension of the device, regardless of how small it is, and ensures device and component biocompatibility.

Parts to be coated are placed in the ambient-temperature deposition chamber and the dimer (raw material Parylene) is placed into the vaporiser at the opposite end of the system. The dimer sublimates and is then pyrolised into reactive monomer molecules. The Parylene monomer enters the ambient temperature chamber and polymerises on the substrate (see Figure 2 over the page).



Calcium (ppm)	Aluminum (ppm)	Zinc (ppm)
0.17	4.2	50
0.15	1.8	35
0.03	0.1	12
<0.002	<0.05	0.2
<0.002	<0.05	<0.05

Figure 1: Effect of Parylene C thickness on extractable metals in rubber specimens.

Because it enters the deposition chamber as a gas, the coating material's penetration power is superb, enabling film to grow on all surfaces and edges uniformly. This includes inside the smallest crevices of a substrate and into the porosity of elastomers – porosity that may be inherently problematic from a tribological standpoint.

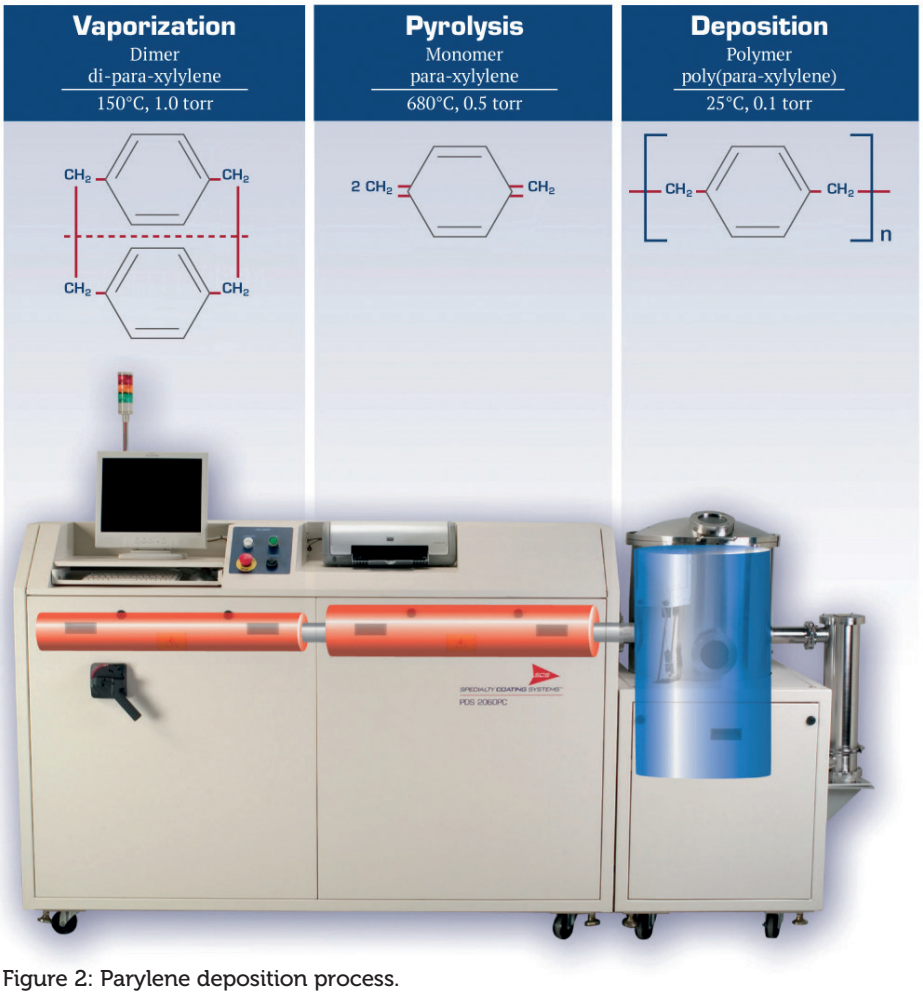


Figure 2: Parylene deposition process.

ISO–10993 BIOLOGICAL EVALUATIONS

	SCS Parylene Variant		
Tests	**N**	**C**	**Parylene HT**
Cytotoxicity	✓	✓	✓
Sensitization	✓	✓	✓
Intracutaneous Reactivity	✓	✓	✓
Acute Systemic Toxicity	✓	✓	✓
Implantation (2 weeks)	✓	✓	✓
Implantation (12 weeks)	✓	✓	✓
Implantation (26 weeks)	✓	✓	✓
Hemolysis	✓	✓	✓
Lee–White Clotting Time	✓	✓	✓
Pyrogenicity	✓	✓	✓

Figure 3: ISO-10993 biological evaluations.

The unique Parylene deposition process allows ultra-thin films to be formed in thicknesses ranging from several hundred angstroms to dozens of microns. Its use has been demonstrated on a host of device classifications that range from surface devices to implant devices, including combination products, e.g. drug eluting coronary stents. Parylene coatings are certified to comply with ISO 10993 as well as USP Class VI biological evaluations (Figure 3).

Whether designers are working on new devices or improving upon existing technologies, one thing remains true: pharmaceutical therapy is continuing to expand both in the technologies offered and conditions treated. As these technologies become more advanced, protection of devices and associated components becomes even more critical. Parylene conformal coatings offer lubricious, biocompatible protection to meet the challenges these devices face, all while increasing functionality and reliability.

ABOUT THE COMPANY

Headquartered in Indianapolis, IN, US, Specialty Coating Systems (SCS) is a leader in Parylene conformal coating services and technologies. As the direct descendant of the companies that originally developed Parylene, SCS has 45 years of experience and expertise that it leverages for its customers through coating facilities throughout the Americas, Europe and Asia.

ABOUT THE AUTHOR

Dick Molin is Medical Market Segment Manager for Specialty Coating Systems (SCS). His focus includes expansion of SCS's medical market activities and new medical applications for Parylene conformal coatings. Molin has over 30 years of experience in product and process development, including 17 years at SCS where he actively worked with advanced materials and processes for Parylene technologies. He earned his Bachelor's degree in Materials Engineering from the University of Arizona and holds a Master of Business Administration in Technology Management from the University of Phoenix.

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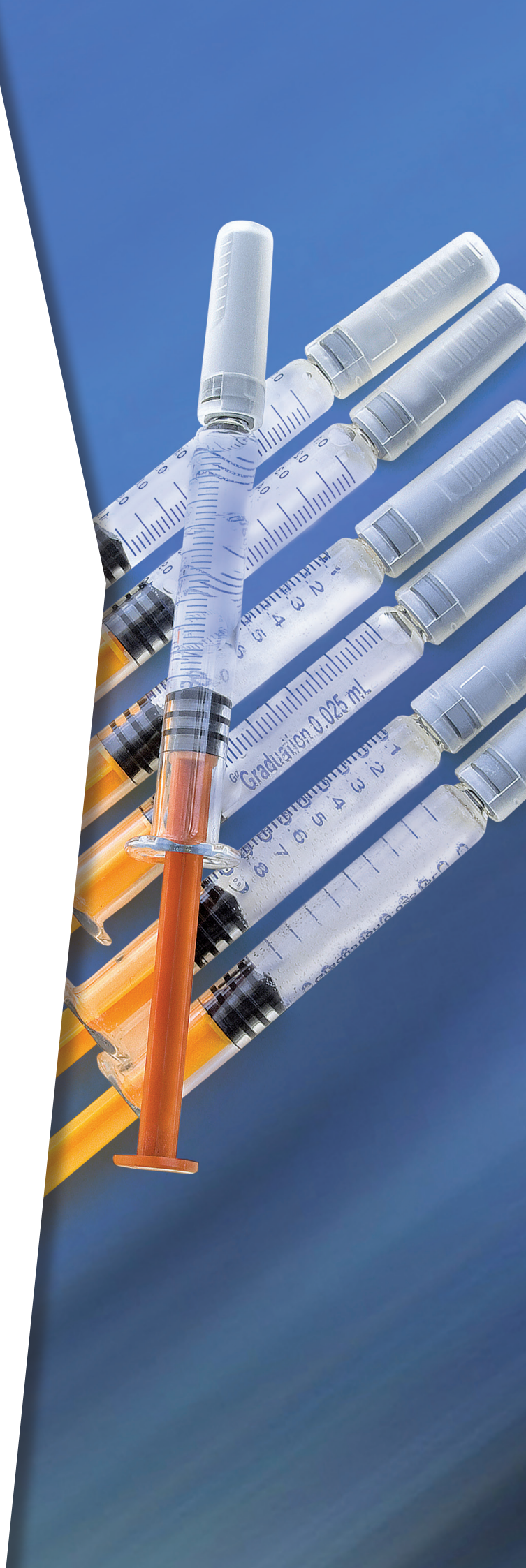
When it comes to reliability, nothing protects like Parylene.

Parylene is an ideal conformal coating for medical and pharmaceutical delivery devices and components. SCS Parylenes can be applied to virtually any material to provide ultra-thin, pinhole-free coatings with superior extractables/leachables barrier properties and excellent non-liquid, low friction/stiction characteristics. Biocompatible Parylene coatings are USP Class VI certified and ISO 10993 tested.

With numerous locations around the world, Specialty Coating Systems is the leader in Parylene coatings and maintains comprehensive FDA Drug and Device Master Files for customer reference.

Contact SCS today for more information about the ways Parylene coatings can enhance the performance and reliability of your medical or pharmaceutical applications.



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