



ENABLING DEVICE INNOVATION THROUGH COMPONENT CUSTOMISATION

In this article, Susan M. Dounce, PhD, Senior Manager, Business Development & Innovation – Injection Systems, Datwyler Sealing Solutions, and Rick Bente, Vice-President, Advanced Drug Delivery Systems, Unilife Corporation, outline Datwyler's offering in the area of customised elastomeric components, in particular for devices containing biologic products. The authors go on to provide Datwyler's collaboration with Unilife for the elastomeric components for its wearable high-volume injection device platform as an example of the successful integration of numerous components into devices, made possible by an increased level of co-operation right along the supply chain.

With the continued growth in the therapeutic biologics industry, there are more drug delivery challenges than ever before. Proteins are inherently susceptible to enzymatic degradation and therefore, in the absence of significant technological advances, therapeutic proteins must be delivered by injection. At the same time, with respect to the parenteral industry, biologic drugs, without question, have the most unmet packaging / delivery needs and therefore the most opportunities for innovation.

As such, there is an increased momentum towards bringing new delivery devices to market which safely and reliably address these challenges and simultaneously optimise the patient experience.

The challenges around the delivery of biologic drugs are largely due to the size and stability of the molecules. As an example, whereas the most comfortable patient experience may be self-administration in a home setting, many biologics are currently administered by intravenous infusion in a healthcare setting. In many cases, this is due to the simple fact that the size of the drug molecules make concentration into a 1-3 mL delivery volume difficult and in some cases impossible. To put things in perspective, a monoclonal antibody with a molecular weight of around 150 kDa is roughly 150 to 1000 times larger than a small-molecule drug. With such large mol-

ecules, as concentration increases, so does formulation viscosity and this can translate into larger dose volumes.

Since self-administration can reduce healthcare costs and increase patient satisfaction and compliance, there is a drive to transition drug administration out of the hospital and directly into the hands of patients – especially for chronic disease states. For biologic drugs, this may require new forms of delivery like a wearable injector system which can administer larger dose volumes over extended periods of time.

Another attribute of biologic drugs which creates delivery challenges is their comparative instability relative to small-molecule drugs. During shipping and storage, biologics can be prone to aggregation, chemical changes like oxidation or de-amidation, and conformational changes. For this reason, it is common for biologics to be stored in a lyophilised form. Although this may be an effective way to handle stability issues, lyophilised products are usually packaged in vials and must be reconstituted at the time of administration by a many-step process which can be complicated and time-consuming.

Reconstitution syringes, which can transform the delivery of a lyophilised drug into a single-step, intuitive and comfortable process, represent a significant advancement in patient-friendly delivery of lyophilised drugs.



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UNCOATED DESIGN



OmniflexCP®

Figure 1: Engineering Expertise – small design changes can significantly impact the performance of a component or the ability to manufacture it. Here, engineers have modified an ISO standard plunger design (left) into a form that gives highly consistent glide forces in a syringe (right).

While such new drug delivery devices like wearable injectors and reconstitution syringes present solutions to some of the unmet needs of biologic drug delivery, they have additional functional features beyond the traditional prefilled syringe and therefore require the seamless integration of dozens of components. Combined with ever increasing regulatory scrutiny, it is this added device complexity that is changing the climate of drug delivery device innovation. Relationships along the entire supply chain are becoming increasingly collaborative – from raw material suppliers to component manufacturers to device integrators to combination product manufacturers.

Also, component suppliers such as Datwyler are experiencing increased demands for customisation. Key to the performance of the integral device is the function of every component and often times, customisation of a single component such as an elastomeric closure, can be a key enabler of device innovation.

SUPPORTING ELASTOMER COMPONENT CUSTOMISATION FOR NOVEL DRUG DELIVERY

With drug delivery device designs becoming more complex, there is an ever increasing demand on each component within the device. Every component, including elastomeric closures, must perform to a high standard and must be effectively integrated with the other device components. By focusing on the core capabilities of engineering, material development and simulation, and quality processing, Datwyler is able to deliver the highest quality, most innovative, customised elastomeric closures to its partners. The seamless interdisciplinary co-operation within Datwyler and the focus on customer collaboration make Datwyler the preferred partner for co-engineering customised solutions.

ENGINEERING EXPERTISE

The mission of the Datwyler engineering team is to drive the smooth and timely transition of products from concept to prototype to mass production - not only for product lines that are proprietary to Datwyler, but also for customer-specific developments. Very often, Datwyler customers are also partners in co-engineering solutions. Tooling Engineering Manager Koen Maes states: “Our customers tell us that what sets Datwyler apart is our flexibility and our timely response. Beyond that, our engineers have a deep understanding of the interaction between elastomer design and processability.”

Indeed, Datwyler engineers are uniquely positioned to identify future production challenges at the concept stage. When starting a new project with a partner, it is common for the initial product design to be tailored to the particular application, but it may not necessarily be optimised for manufacturing. Some design changes can have a significant impact on performance (as in Figure 1) or the ability to scale-up production. “It might not look like a big

MATERIAL EXPERTISE & SIMULATION

Datwyler continues to lead the industry when it comes to developing the cleanest and best performing elastomer compounds and coatings. As the scrutiny around leachables and particulates from parenteral packaging components continues to escalate, Datwyler material developers advance the industry standards in elastomeric closure cleanliness by a three-part approach:

1. to develop next-generation elastomer compositions that are inherently cleaner
2. to understand and manage the raw materials used in the compounds and coatings
3. to develop and optimise low-particulating, lubricious barrier coatings such as Omniflex.

Datwyler’s proprietary Omniflex coating which significantly reduces subvisible particle levels, is inherently well-suited for creating custom designs that are barrier coated. “The flexibility and scalability of our Omniflex technology makes it the only technology that offers a very short iteration loop for customised coated product

“Relationships along the entire supply chain are becoming increasingly collaborative – from raw material suppliers to component manufacturers to device integrators to combination product manufacturers”

deal but sometimes a minor alteration to a radius of curvature or a cavity diameter can make all the difference when it comes to industrialisation,” says An Vanheel, Project Manager. This expertise is critical to optimising customer-specific designs and Datwyler’s open collaboration is one key to co-engineering success.

development and hence offers, in the end, a speed-to-market benefit,” says Dr Bram Jongen, Head of Material Development. “Datwyler is equipped to coat a few hundred products up to full-blown production of millions per year.”

Combining Datwyler’s best-in-class materials with customised, optimised

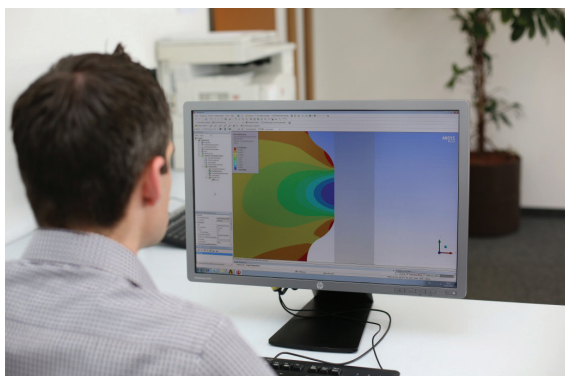
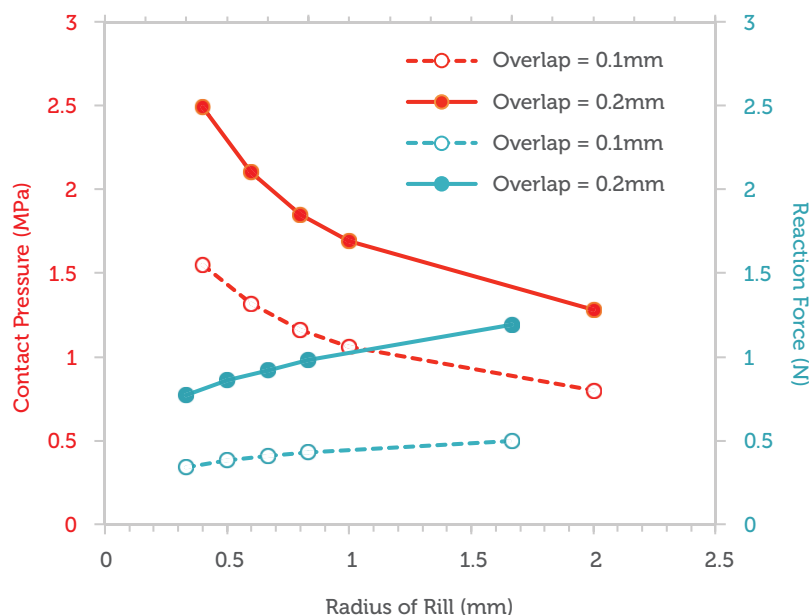


Figure 2: Material Expertise & Simulation – Datwyler continues to develop the industry's cleanest and best performing elastomer compounds and coatings and Datwyler's material expertise is complemented by simulation capabilities. Here, experts in Finite Element Analysis simulation construct a qualitative model to depict the influence of syringe barrel and plunger rill diameters on contact pressures and reaction forces.



designs leads to products with outstanding performance. Finite element analysis (FEA) facilitates a fundamental understanding of the properties and functionalities of products and provides a basis for improving product performance. “The keys to building reliable FEA models with predictive power are the use of the most accurate physical and mechanical input parameters, and the alignment of the simulation results with well-understood experimental data”, says Rudolf Randler, Head of Material Development for New Products & Simulation. “This involves high quality measurements for the determination of the material properties of Datwyler elastomers and also requires the design and execution of well-controlled, statistically sound testing.” The Datwyler simulation team uses qualitative and quantitative FEA results to understand better how material properties and design changes can impact product processability or performance (as in Figure 2), and the team is available to aid in the optimisation of customised co-engineering solutions.

PROCESSING QUALITY

FirstLine® is Datwyler's state-of-the-art manufacturing facility (Figure 3) located in Alken, Belgium which is dedicated to the production of high quality pharmaceutical closures. Today, primary packaging component manufacturing is considered to be an extension of the drug manufacturing process itself and the FirstLine® facility was designed to meet the evolving standards of the parenteral industry. The facility design, process flow, gowning protocols, personnel and material flow, camera inspection, and automation all result in the lowest endotoxin, bioburden, particulate, and defect levels available in the industry. The production of custom-designed elastomer products for pharmaceutical packaging can be located within the FirstLine® facility upon request.

By focusing on and excelling at these core capabilities, Datwyler is able to deliver the highest quality elastomeric closures for new drug delivery devices. Flexibility, customer focus, and interdisciplinary cooperation make Datwyler

the preferred partner for collaborative developments.

CASE STUDY IN ELASTOMER DEVELOPMENT: UNILIFE WEARABLE INJECTOR PLATFORM

A growing multitude of pharmaceutical and biotechnology companies have large portfolios of biologics, such as monoclonal antibodies, that require the subcutaneous self-administration of large dose volumes over periods longer than is suitable for the use of hand-held devices. To accommodate the specific drug and patient needs of each molecule in the portfolio, many pharmaceutical companies are seeking to select one platform-based wearable injector technology that is simple to customise, commercialise and use.

Unilife, a US based designer, developer and supplier of injectable drug delivery systems, has created a broad, flexible portfolio of wearable injectors (see Figure 4) that allows pharmaceutical customers to bring to market each molecule with minimal risk and maximum user preference. In addition,



Figure 3: Processing Quality – FirstLine® is Datwyler's state-of-the-art manufacturing facility for elastomeric closures designed to provide the lowest endotoxin, bioburden, particulate, and defect levels available in the industry.



Figure 4: The Unilife Wearable Injector Platform – Unilife has created a broad, flexible portfolio of wearable injectors that allows pharmaceutical customers to bring each molecule to market with minimal risk and maximum user preference.

Unilife Requirement	Datwyler Solution
Chemical compatibility with biologic drugs	Material Expertise – Omniflex fluoropolymer coating technology for superior chemical compatibility and the elimination of silicone-oil-based subvisible particles.
Low subvisible particle levels	
No new production processes	Engineering Expertise – Fast, flexible, customer-centered design engineering for rapid transition from prototype to production of custom designs. Processing Quality – State of the art processes and production facilities with turnkey solutions to accommodate custom designs. Processing Quality – State of the art processes and production facilities with turnkey solutions to accommodate custom designs.
Less than 6 months to validated production runs for custom designs	

Figure 5: Four key programme requirements for Datwyler elastomeric closures in the Unilife wearable injector platform.

tion to the company's wearable injectors being prefilled, pre-assembled and ready-to-inject, they can be fully customisable to address specific drug and patient requirements including dose volume, duration rate, drug viscosity and Bluetooth connectivity. Like all of its platforms, Unilife also works with customers to select standard primary container materials and components from a range of preferred suppliers.

As part of its customer-centric strategy to leverage well understood materials and ensure systems are supplied ready for seamless integration with approved filling and packaging processes, Unilife entered into a collaborative development programme with Datwyler to design and manufacture customised elastomeric components for the Unilife wearable injector platform. Unilife's device and primary container expertise and Datwyler's deep understanding of elastomers have together resulted in a new septum and plunger system which meets the exacting specifications of the Unilife design and provides the value of Datwyler's bromobutyl elastomer and Omniflex fluoropolymer coating technologies. The system is validated and available for use in commercial and stability programmes.

Key Requirements for Elastomeric Closures in the Unilife Wearable Injector

In entering into the collaborative partnership, Unilife identified a number of key programme requirements for elastomeric closures in the wearable injector system. Four of these are shown in Figure 5 together with Datwyler's solutions.

Both the custom designed plunger and septum are coated by Datwyler's proprietary Omniflex inert fluoropolymer spray coating technology. This enables the elastomeric closures to meet the first two key programme requirements. The Omniflex fluoropolymer coating is the first coating to simultaneously provide barrier properties and to eliminate the closure as a source of silicone-oil-based subvisible particles. As a consequence of the coating's chemical composition and method of application, Omniflex Coated Plungers (OmniflexCP®) not only have barrier properties that result in superior chemical compatibility but have the added benefits of a significant reduction in subvisible particle levels and highly consistent delivery forces.

The other two programme requirements were the use of existing processes and scaling up within six months to ensure speed to mar-

"Key to the performance of the integral device is the function of every component and customisation of a single component such as an elastomeric closure, can be a key enabler of device innovation."

ket with minimum risk to the combination product manufacturer. Although the product designs are customised, the septum and plunger production, coating, washing, and sterilisation are standard, turnkey processes.

Key Attributes of the Plunger and Septum

The overall functional performance and chemical compatibility of the Unilife wearable injector are influenced by the Datwyler elastomer components. The proprietary septum and plunger (as in Figure 6) that are used in the Unilife wearable injector platform have been developed using the Datwyler FM257 / FM259 bromobutyl elastomer platform.

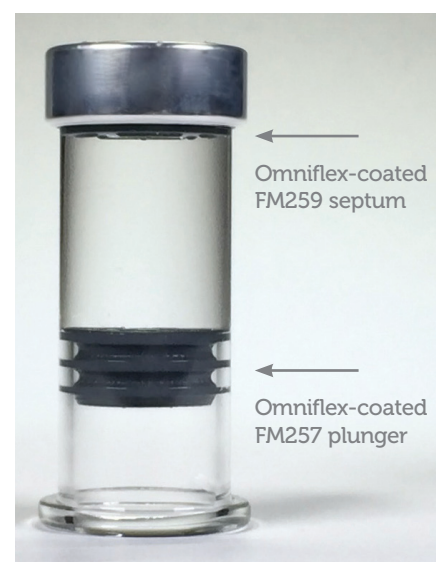


Figure 6: Datwyler Elastomeric Closures for the Unilife Wearable Injector Platform – The collaborative program between Datwyler and Unilife has resulted in a new septum and plunger system designed to meet the demanding specifications of the Unilife wearable injector platform. The customised elastomeric components are coated with the Omniflex fluoropolymer coating technology which results in low extractable levels, low subvisible particle levels and highly consistent delivery forces.

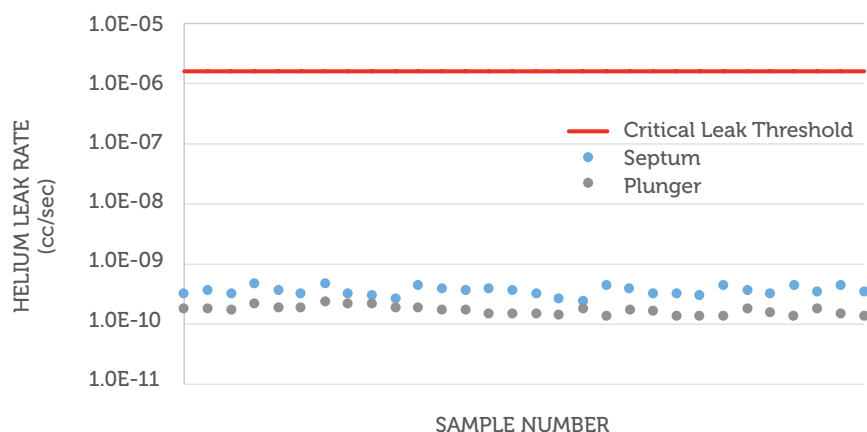


Figure 7: Container closure integrity: helium leak test results from 30 different septa samples (blue) and plunger samples (grey) assembled in the glass barrel. The leak rates are more than three orders of magnitude lower than the critical leak threshold (red line) defined by Kirsch et al.

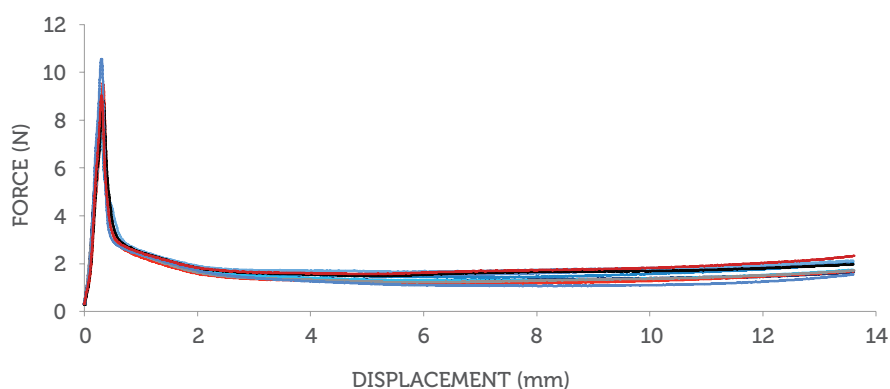


Figure 8: Delivery force profiles from ten different empty Unilife wearable injector samples. The highly consistent profiles are attributable to the Omniflex coating technology along with the optimised plunger design.

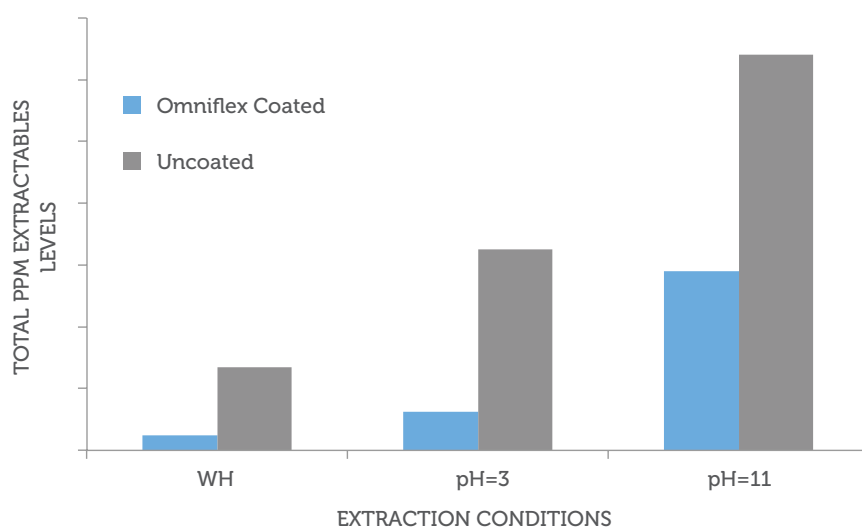


Figure 8. Relative elastomer extractable levels from an uncoated FM257 bromobutyl plunger (gray bars) as compared with Omniflex coated plunger (blue bars).

"The overall functional performance and chemical compatibility of the Unilife wearable injector are influenced by the Datwyler elastomer components"

With the same base formulation ingredients, the FM257 rubber is designed to be harder and well-suited to plunger applications and the FM259 rubber is designed to be softer and shows exceptional fragmentation and resealing properties. Lab-scale Omniflex coating capabilities enabled rapid prototyping of early design iterations prior to scale-up to full production. Some of the key chemical and functional properties of the injector platform which are influenced by the elastomeric closures are discussed below.

Container Closure Integrity

Container closure integrity is the most basic requirement of an elastomeric closure for parenteral packaging. Helium leak testing on each closure used in the wearable injector, as shown in Figure 7, revealed results of $3.6 \times 10^{-10} \text{ cm}^3/\text{s}$ for the septum and $1.7 \times 10^{-10} \text{ cm}^3/\text{s}$ for the plunger assembled in the glass barrel. These values are more than three orders of magnitude lower than the critical helium leak rate considered to be correlated to microbial ingress ($1.6 \times 10^{-6} \text{ std cm}^3/\text{s}$) (Kirsch et al, PDA J Pharm Sci Tech, 1997, Vol 51, pp 195-207).

Low Dead Volume

Especially for biologic drugs which can cost thousands of dollars per dose, ensuring a low residual volume is an essential attribute of any injection device. The proprietary custom designs of the wearable injector's plunger and septum enable the residual volume to be less than 100 μL , with nominal values ranging between 30-50 μL .

Consistent Delivery Forces

Consistent delivery forces are an important factor in minimising the variability in injection times. Due to both the absence of silicone oil and to the optimised plunger design which eliminates the trim edge, the Omniflex coated plunger has highly consistent delivery forces from three perspectives:

- 1) consistent forces as a function of displacement (i.e. no stick-slip behaviour)

- 2) consistent forces from plunger to plunger
- 3) consistent glide forces with aging.

Figure 8 shows the force profiles for ten different empty wearable injector samples. The break-loose forces are typically less than 13 N and glide forces are less than 2 N.

Low Extractables

An advantage of the Omniflex spray coating process is that, in contrast to most film coatings, the entire surface of the bromobutyl closure that is in contact with the container walls and drug product, is barrier coated. As Figure 9 shows, the Omniflex coating is designed both to reduce the number and levels of extractable species from the base rubber including, especially, metal ions.

Elimination of Silicone-Oil-Based Subvisible Particles from the Elastomers

One of the largest sources of subvisible particles in prefilled syringes is silicone oil and studies have shown that the plunger can be a larger source of free silicone than compared to the barrel. (Felsovalyi et al, J Pharm Sci, 2012, Vol 101(12), p 4569.) The Omniflex coating is lubricious and does not require

siliconisation. As such, and as demonstrated by Felsovalyi et al, there is an absence of silicone-oil-based subvisible particles migrating from an Omniflex-coated elastomer and an overall reduction in particle levels of up to 95% versus components siliconised with a low viscosity oil.

No Coring

The septum designed for the Unilife wearable injector utilises the Datwyler FM259 bromobutyl compound in combination with the Omniflex coating. This rubber has a hardness of 39°ShoreA which enables excellent fragmentation and resealing properties. Furthermore, the Omniflex coating stays intact upon puncturing without tearing or wrinkling as may be experienced with a traditional film coating. The septum easi-

"The successful integration of the many components in these devices requires an increased level of co-operation along the entire supply chain"

ly meets the coring requirements of ISO 11608-3 (Needle-based injection systems for medical use – Requirements and test methods – Part 3 – Finished containers.)

SUMMARY

Devices like wearable injectors and reconstitution syringes (the subject of another on-going Datwyler-Unilife collaboration) represent significant innovations in the delivery of biologic drugs and are well-positioned to improve the patient experience. The successful integration of the many components in these devices requires an increased level of co-operation along the entire supply chain. Flexibility, customer focus, and interdisciplinary co-operation make Datwyler the preferred partner for collaborative developments.

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