BESPAK
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THE CHANGING FACE OF AUTOINJECTOR TECHNOLOGY

In this article, Reenal Gandhi, Business Development Director, Bespak by Recipharm, discusses the advantages offered by liquefied gas as a power source for autoinjectors compared with conventional spring-based systems, as well as covering the benefits of using a platform model for drug delivery device development.

Over the past 20 years, drug delivery via an autoinjector has helped improve the patient experience and increase treatment adherence, with this trend continuing today. The autoinjector market has been growing, providing an easier alternative for patients to self-administer treatments that would otherwise be given by a healthcare professional. An autoinjector is often used to reduce dosage errors associated with self-administration, to alleviate patient concerns relating to needle phobia and to combat dexterity challenges. Typically, self-injections with autoinjectors are recommended to take less than 10–15 seconds to complete but with high viscosity products this can pose a challenge.

OPTIMISING INJECTABLE DRUG DELIVERY

The injectable drug delivery market is expected to grow from US$362.4 billion (£280.6 billion) in 2016 to $624.5 billion (£483.6 billion) by 2021.[1] This growth is, in turn, helping to drive the global autoinjector market size, which is expected to be worth in the region of $3.2 billion (£2.5 billion) by 2026, growing at a compound annual growth rate of 19.6% between 2019 and 2026.[2]

This rapid growth is driven by many factors. There has been an increase in the number of treatment options for chronic diseases involving biologics. In an effort to increase patient care and remain competitive in the growing biologics market, more products are moving towards reducing injection frequency, which often leads to increased concentration and higher viscosities.

There are also significant cost benefits to be achieved by healthcare providers in moving the administration of some medicines out of the clinic and into patients' homes. In addition, a greater market acceptance and transition to autoinjectors has been fuelled by increased convenience and ease of use.

Many biologic therapies are monoclonal antibodies that require high doses, resulting in high-viscosity liquids which are challenging to inject with a syringe or typical spring-based autoinjector. Using a device to appropriately deliver the product demands a complex and balanced combination of power to apply the necessary force, while managing the forces applied to fragile components, such as the syringe.

Novel autoinjectors are emerging to address these needs, delivering substantial benefits for both patients and drug developers.

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NOVEL ADVANCEMENTS IN AUTOINJECTOR DESIGN

Today, the use of liquefied gas, such as liquefied hydrofluoroalkane (HFA), as a power source for autoinjectors has presented several benefits over traditional spring-driven devices. One of the main advantages is that it provides a near constant force over the duration of the injection. To achieve full injection, HFA-powered autoinjectors require lower peak forces compared with a typical spring autoinjector because the force does not decay. This applies lower stresses on the syringe and results in lower variation of force during drug delivery.

Figure 1 shows how an HFA-powered device provides a constant force and stopper velocity. As the liquefied HFA converts to gas, the expansion leads to a soft start of injection. The initial force peak can be much lower compared with a spring. As the gas continues to expand, the stopper velocity remains near constant, providing a steady force as the complete dose is injected. This is a major advantage compared with a spring-based autoinjector's kick start, where the spring can apply a high impact to the syringe. The resulting forces are centralised to weaker locations, such as the syringe flange or shoulders, increasing the chance of a breakage. For example, with technologies such as Bespak's VapourSoft, the forces are contained within the can until the device is used, which virtually removes any long-term loads on the device components compared with a conventional spring-based autoinjector.

Figure 2 demonstrates the steady pressure afforded by HFA-powered autoinjectors for a more constant rate of injection.

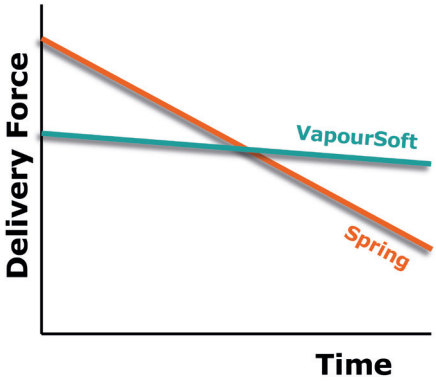

Figure 1: Change in force applied to a syringe in an autoinjector with a standard spring (red) and a liquified gas-powered system such as Bespak's VapourSoft (blue).

ADAPTING TO CHANGING REQUIREMENTS: ADDRESSING THE NEED FOR FLEXIBLE PLATFORMS

The development of an autoinjector traditionally proceeds through several stages:

- Concept evaluation and feasibility
- Product validation
- Transfer to manufacturing
- Scale-up.

By leveraging a platform development, these "off-the-shelf" options can now offer drug developers multiple configurations that allow for fast changes to a device according to the needs of a specific therapy. For example, a liquefied gas-powered autoinjector has the advantage that different force profiles can be obtained by simply changing the HFA gas, making it easy to adapt the platform to different drug products and different fill volumes without requiring complicated and lengthy device customisations.

When working with a platform, development has undergone the iterative process of prototyping, analysis and design modification to produce a reliable product. Designers work with an array of drug formulation properties, such as flow, viscosity and volume, and functionality requirements, including end user needs and scalability, to drive the design input requirements. Prototyping and technical guidance is a crucial element of the development process to ensure all components can be robustly scaled up for high-volume production.

Progress at every stage of production must be evaluated via a gated review by the programme team and key stakeholders to decide if the criteria to progress to the next stage have been fulfilled. This helps ensure a smooth transition from early-stage design to commercial manufacture. By performing design reviews, adjustments can be identified to help define the specification and build the process parameters.

The process parameters will be defined from the learnings during the development as products transition from prototype to small scale. This opportunity to work at a low-volume scale means that adjustments can be made to study performance, building confidence in the product capabilities. As products progress to higher volumes, process scalability needs to be proven. In most programmes, a stepwise approach will allow

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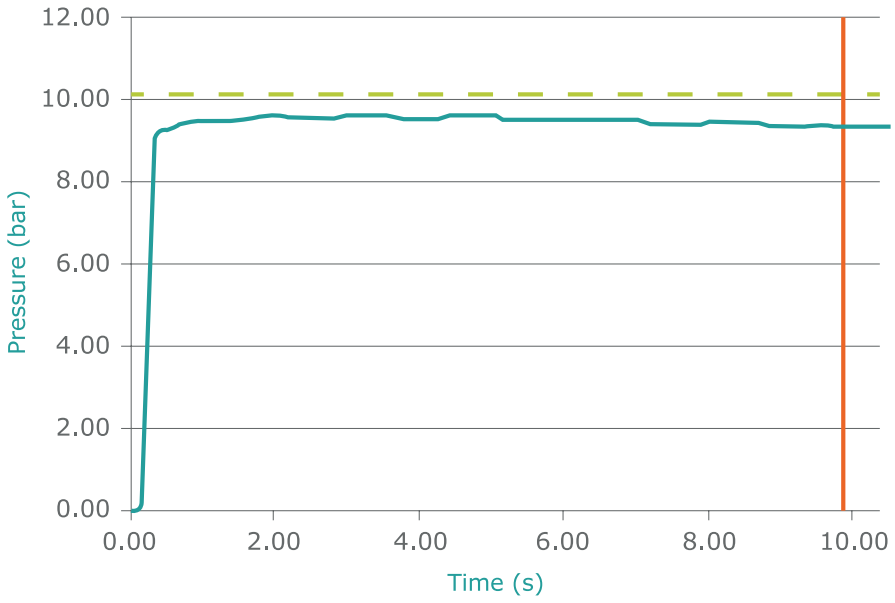

Figure 2: Pressure in a liquefied gas-powered autoinjector during injection.

for smart process design and predictable results. Working with a device partner that has the experience and capabilities to take the device design platform through to full scale and commercial manufacturing provides experience and development that can be flexible enough to meet unique product needs.

During pharmaceutical development, once a device requirement has been integrated, it can then be streamlined by analysing filled syringes and then assembling them into an autoinjector to study performance and identify potential areas for product-specific adjustments. By using the platform approach to design, the validation requirements of the final device are then based on a risk assessment of the gap between the basic device and the drug-specific variation. This type of approach can ensure that specifications are designed appropriately to ensure a drug product and device work together in the best possible way, while reducing the necessary time and resources for development.

REGULATORY AND QUALITY CONSIDERATIONS

Regulatory requirements should be incorporated from the initial stages of product development, as doing so will help to ensure that submission processes are as straightforward as possible further down the line. Requirements to be met include 21CRF820.30 and ISO 13487 for design control parts and ISO 10933 materials compliance, as well as the ISO 11608 series of standards specifically for autoinjector products, amongst several other more specific standards and industry guidance.

The complexity of a combination product filing and the level of detail regulatory agencies need is important to consider up front. Drug developers will want to work with partners that are able to support them during the filing phase and have proven experience of dealing with regulatory aspects. Rigorous in-process testing should also underpin all operations to provide the highest levels of style guide says no need to define – so just cGMP control, regulatory compliance and quality.

For example, in the US, vendors should be able to supply a medical device master file (MAF) filing which will contain all the detailed device information. The MAF can be used in the submission approach or, alternatively, the device information can be included within the drug product filing itself. This judgement should be made based on several factors, including the level of device experience within the pharma company and the regulatory strategy. One benefit of an MAF filing is that any device-related questions from the US FDA can be directed to the device partner, who will be able to provide answers to the device questions based on their prior experience of dealing with the FDA.

LOOKING TO THE FUTURE

Longer lifespans and greater numbers of patients being diagnosed with chronic conditions are calling for greater significance to be placed on the self-administration of medications. In line with this, more drug developers are looking to improve therapies to reduce dose frequency, achieve better convenience and ensure comfortable delivery for patients. The industry is increasingly realising that the success of products no longer relies solely on the therapeutic success of the drug itself, but on maintaining patient satisfaction and adherence.

As the sector continues to evolve, further advances will be forthcoming. There is a great opportunity for connectivity to be incorporated into devices, with steps towards these capabilities already being made by many device developers. This will make it possible to monitor injection data through data analytics and visualisation portals to help improve medication regimes.

In addition to higher concentrations, new drug formulations are also trending towards higher volumes (greater than 3 mL). Device vendors are now also addressing the market needs for high-volume injection devices.

The autoinjector market has established itself as a promising sector within the pharmaceutical industry. With improved capabilities of platforms and better understanding of regulatory processes, we are going to see more and more therapies delivered via autoinjectors, which is a positive step for patients living with chronic diseases.

ABOUT THE COMPANIES

Bespak by Recipharm delivers market leading design, development and manufacture of drug delivery devices to the global pharmaceutical market. This includes inhaler, nasal technologies and autoinjectors, as well as development and manufacturing services. Bespak's VapourSoft® platform offers full flexibility and capability to deliver high-viscosity formulations with ease. Syrina®, a VapourSoft®-powered autoinjector, has completed design verification testing and low-volume commercial and clinical supply is now available.

Recipharm is an innovative drug delivery device company. Driven by customer and patient demand, Recipharm's innovations have the potential to create new treatments and opportunities across the globe, as well as accelerating routes to market.

REFERENCES

1. *"Injectable Drug Delivery Market by Type (Device, Formulation), Therapeutic (Cancer), Usage Pattern (Immunization), Administration (Skin, Musculoskeletal), Distribution Channel (Hospital), Patient Care Setting (Hospital, Home Care) - Forecast to 2021". Market Report, Markets and Markets, February 2017.*
2. *"Auto-Injectors Market (By Product Type: Disposable Auto-Injectors, Reusable Auto-Injectors; By Disease Indication: Rheumatoid Arthritis, Multiple Sclerosis, Diabetes, Anaphylaxis, Other Therapies; By End-use: Home Care Settings, Hospitals & Clinics, Ambulatory Surgical Centers) - Global Industry Size, Share, Trends and Forecast 2019 - 2026". Market Report, Acumen Research and Consulting, 2018.*

ABOUT THE AUTHOR

Reenal Gandhi is Business Development Director at Bespak by Recipharm and has more than 15 years' experience in both the drug delivery device and pharma industry, developing and commercialising drug delivery solutions for biotech, vaccine and pharma. She has an MBA and has experience in business development and licensing for innovative and generic products. Ms Gandhi is responsible for business development activities related to nasal devices and injectable devices such as autoinjectors and wearable injection systems.