COMBINING HUMAN NEEDS WITH HIGH VISCOSITY FORMULATIONS

In this article, Jonathan Bradshaw, Device Development Engineer, and Susie White, Mechanical Engineer, both of Oval Medical Technologies, discuss the requirements of designing an autoinjector capable of handling the high pressures necessary for the delivery of highly viscous drug formulations with minimal impact on the patient.

INTRODUCTION

> "When endeavouring to deliver HV formulations, there exists a delicate balance between the needs of the patient and those of the device mechanism."

Within the injectable drug landscape, the availability and usage of high viscosity (HV) drugs is growing, often driven by developments such as long-acting injectable (LAI) technologies. Currently, these products provide significant advantages in terms of more convenient dosage volumes for patients and healthcare professionals (HCPs). With a trend towards self-administration, LAIs allow for less frequent dosing thus promoting better patient compliance.[1]

Typically, LAI products consist of formulations that are highly viscous in nature (100–1000 cP), can present non-Newtonian and, in the case of suspensions, "clogging" characteristics. These characteristics are well beyond the normal limits of injection devices and techniques, presenting many challenges for subcutaneous (SC) and intramuscular (IM) drug delivery.

When endeavouring to deliver HV formulations, there exists a delicate balance between the needs of the patient and those of the device mechanism. From a device perspective, there are many ways in which HV delivery can be achieved, such as through larger needle diameters, longer delivery times and larger spring forces. However, all these approaches risk reducing patient acceptability due to an increase in pain, lack of usability and the resulting large, noisy devices.

To achieve HV delivery both acceptable to the patient and within the capability of the device mechanism, device developers can manipulate parameters such as injection speed, needle gauge or drug volume. Altering these parameters must be approached with caution however, as they can significantly affect bolus formation and therefore the desired pharmacokinetic profile.

Figure 1: ArQ™ Bios: Oval's high viscosity platform provides the ability to meet both patient and drug requirements.

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To maximise user benefit when delivering HV formulations, it is imperative that a "human" solution to autoinjector design is achieved. For certain patient populations this means smaller needle gauges and shorter delivery times are required, both of which can be facilitated using large, controlled forces. This results in a major challenge for devices due to the high internal pressure this generates.

Oval has managed to address this high internal pressure requirement within its HV delivery platform, ArQ™ Bios (Figure 1).

BALANCING THE VARIABLES

Generally, there are four key inputs that should be considered when developing an autoinjector mechanism capable of delivering high viscosity drugs:

1. Drug viscosity
2. Drug volume
3. Needle gauge
4. Delivery time.

These variables are key in determining the ability of the device to deliver highly viscous drugs and are crucial in defining the likely effect of the injection process on the user. When administering LAIs, it is imperative that these variables are tuned to produce consistent bolus characteristics. There is a potential for the surface area of the bolus formed on injection of LAIs to affect the pharmacokinetics of the drug. In such a case, consistent bolus formation is key in achieving the desired pharmacokinetic profile and therapeutic effect.[2]

When developing an autoinjector mechanism to achieve this, the main output from these variables for the design process is internal container pressure, which is produced by the power source acting on the plunger. Using a modified form of the Hagen-Poiseuille equation we can calculate the internal pressure necessary to deliver a given formulation:

$$P = \frac{128\mu LV}{\pi D^4 T}$$

P – Drug Pressure
L - Needle Length
μ - Viscosity
D - Internal Needle Diameter
T – Delivery Time
V – Volume

Modified Hagen-Poiseuille Equation.[3]

This internal pressure has a direct effect on the required strength of the primary drug container (PDC), and is therefore key within the device development process. When delivering a drug of a fixed viscosity, inputs can be manipulated to reduce the sensitivity of PDC design to internal pressure. However, altering user-perceivable inputs such as needle gauge, delivery time and volume should be approached with significant consideration to the user experience. When delivering highly viscous drugs, a simple approach would be to increase the needle diameter, thus reducing pressure. However, a larger needle would result in greater injection pain and negative visual perception by the patient. On the other hand, using a smaller needle would indeed reduce injection pain, but delivery time and risk of jetting would increase, again leading to a poor user experience.

It is possible to manipulate viscosity to aid delivery within patient-acceptable parameters, however with bolus formation key to ensuring drug metabolism, and therefore efficacy, this should also be approached with caution. Typically, formulation viscosities tend to be proportional to drug concentration, i.e. as viscosity decreases, volume must increase to achieve the same therapeutic effect, and vice versa.

THE IMPORTANCE OF DRUG CHARACTERISATION

LAI products are formulated to provide a specific therapeutic effect that is supported over monthly, bimonthly or, in some cases, three-monthly dosing regimens.[4] To achieve this, formulators can reduce the solubility of the LAI, facilitating a sustained and controlled release of drug over time. Currently there are three key approaches to developing slow release formulations:[2]

- Oil solutions
- Polymeric barriers
- Crystalline water-insoluble suspensions.

These approaches or "vehicles" are typically of high molecular weight, which in turn increases the viscosity of

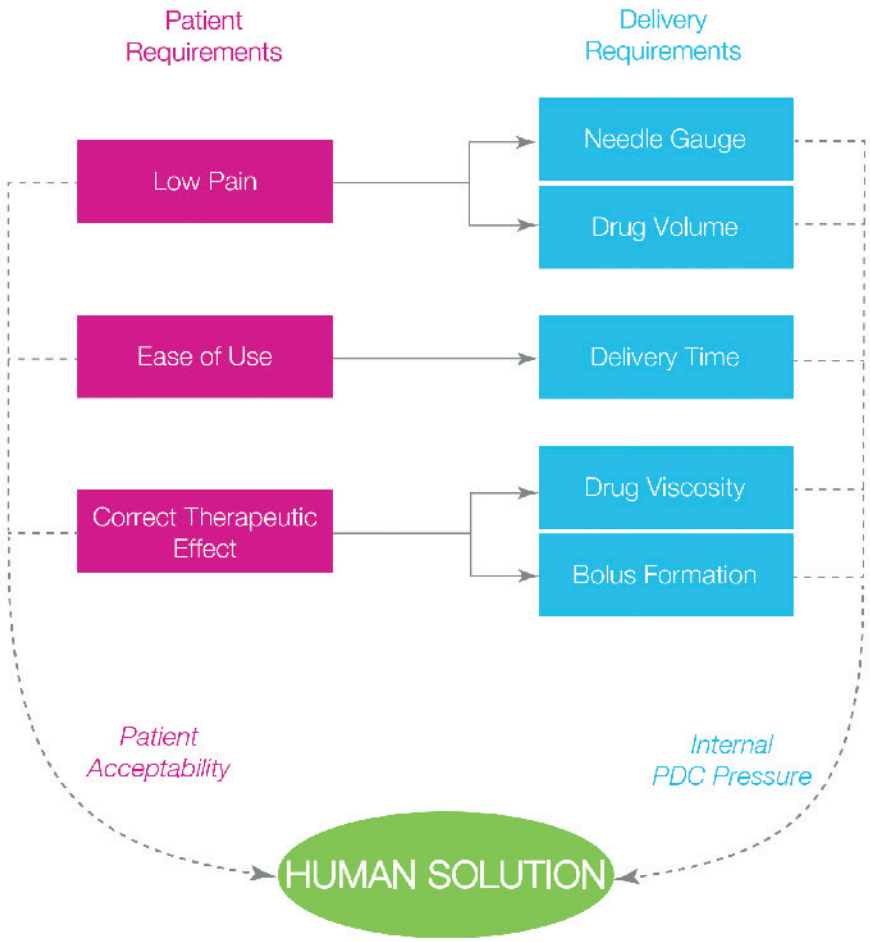

Figure 2: To maximise patient benefit, delivery variables must be influenced by a patient-orientated specification. This often results in increased pressure requirements for the PDC.

the entire formulation. This can lead to non-Newtonian behaviour and increased sensitivity to environmental conditions. Additionally, delivering these via autoinjector can be further complicated by other characteristics, such as clogging and settlement during storage in the case of suspensions. This puts great onus on the delivery mechanism to overcome or manage the delivery requirements of a formulation.

When developing an autoinjector mechanism that can deliver a drug in a time frame and manner acceptable to the patient, it is imperative to fully understand the flow characteristics of the formulation. Through implementing a full characterisation programme early within the device development process, any difficult or undesirable delivery characteristics will be quickly revealed. This allows developers the understanding necessary to manipulate delivery variables effectively, ultimately resulting in a device which is considerate of both patient and formulation requirements.

AN OPTIMAL DRUG DELIVERY SPECIFICATION FOR THE PATIENT

The requirements for HV delivery and patient acceptability can often conflict. However, achieving a suitable balance between the two provides the opportunity to create a truly "human solution" to HV delivery.

A range of factors can influence the acceptability of a device to a patient. As part of achieving a device which maximises patient acceptability, it is key to define a delivery specification which maximises benefit to the patient whilst also overcoming the challenging nature of the drug. The relationships between patient and drug requirements can be broadly defined as shown in Figure 2.

Typically, there are three key patient-perceivable inputs, needle gauge, delivery time and volume, which can be optimised to deliver highly viscous drugs in a manner deemed acceptable to patients:

- **Needle gauge**: The width of a needle can have an impact on the perceived pain of injection.[5,6] Generally, reducing needle size can reduce pain and increase patient acceptance, however needle selection is dependent on numerous factors such as formulation, administration route and intended patient population.[7] Often there exists a trade-off between minimising injection pain and overcoming common issues such as clogging or achieving the required needle strength. Ultimately, for IM injections, gauge choice is usually limited by needle strength, and those narrower than a 23G needle are infrequently used. If a SC route is required, then much narrower needles can be utilised (e.g. 25G), however here the drug flow requirements are more likely to be the limiting factor. It is important to balance adequate needle strength for application with pain perception and the required flow rate for highly viscous drugs.[6,8,9]
- **Delivery time**: With high viscosity drugs, flow rate and therefore delivery time is key in ensuring adequate depot/bolus formation.[8] Shorter injection times (<1 sec) can risk jetting and an undesirable bolus formation whereas longer injection times (>10 sec) can negatively impact patient acceptance. Although flow rate can have varying impact on perceived pain,[10,11] there are indications that longer injection times can prolong pain from needle insertion itself, thus reducing patient acceptance.[7,11,12] Ultimately a delivery time acceptable for both bolus formation and patient tolerability is desirable.
- **Volume**: Typically, LAIs range in volume from 1–3 mL, with lower volume injections being generally better tolerated in SC applications.[10,13,14] Interestingly there are indications that higher viscosity products can improve pain perception,[12] although this is likely dependant on other variables such as active ingredients, pH and temperature.

For highly viscous formulations, increasing the internal PDC pressure is of clear benefit to the patient (Figure 3).

To balance device, drug and patient requirements, Oval Medical Technologies has developed an ideal user-orientated specification which forms a lightweight framework for maximising patient acceptability of high viscosity autoinjectors:

- 3–5 second delivery time
- 23G needle (IM), 25G needle (SC)
- 3 mL maximum volume
- 1000cP maximum viscosity.

Using this specification, analysis has shown that a pressure of 100 bar would be required within the PDC for a 5 second delivery, however pressures of this magnitude are normally beyond the capability of most traditional glass containers. The ability to manage these pressures would create benefit to patients in addition to HCPs and formulators alike.

OPTIMISING PDC LOADING

Developing a PDC with the ability to withstand pressures of up to 100 bar poses huge design challenges for device developers, due to the risk that pressures of this magnitude have on effective and safe delivery. The loading of the PDC is a key factor to consider during development, although very high pressures are required to

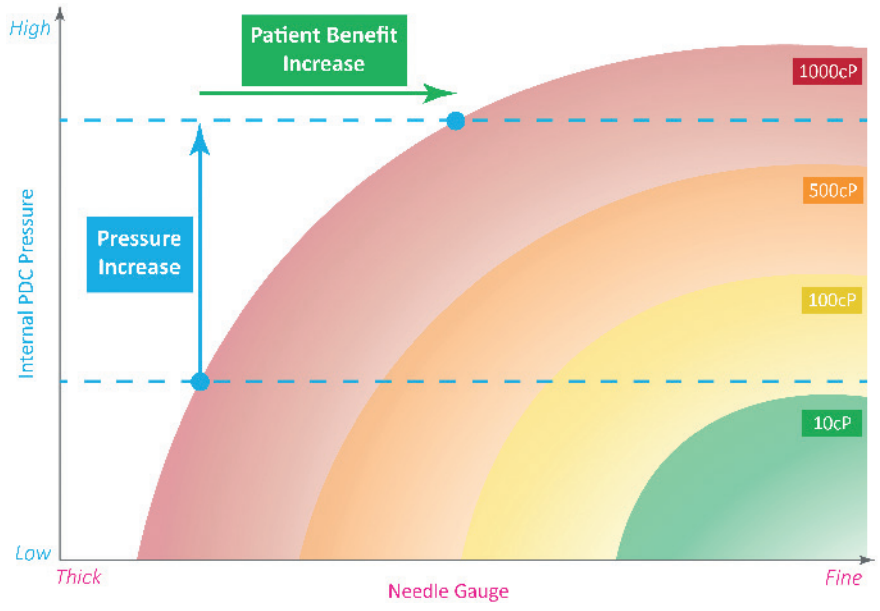

Figure 3: Increasing the pressure loading within the PDC allows for improved patient benefit through use of finer needle gauges at fixed viscosities.

deliver viscous products, developers must consider how the PDC is loaded within the device and whether stress is unnecessarily applied to the container.

A good example of this is the impact that can be exerted on a PDC at the start of delivery. Most autoinjectors are powered by springs held in a compressed state until the point of activation. At activation, the spring force is suddenly released which can cause serious problems for components which bear the brunt of this force – typically the PDC. This issue can be further compounded when manufacturing tolerances lead to excessive clearance between device components, allowing the spring to build up momentum. This momentum must then dissipate upon collision with the PDC, causing a brief but large spike in internal pressure, resulting in additional burden on an already highly stressed component.

It is important not to underestimate the benefits of reducing impact loads, indeed many materials respond differently to shock loading than they do to static loading. Dependent on material, many components will be capable of managing loads when applied progressively, yet when the same force is applied instantaneously there is little time for energy to dissipate and a brittle failure is more likely to occur. With some careful design consideration, it is possible to reduce this effect or eliminate it entirely.

When developing a high viscosity PDC, Oval has employed three strategies to manage the effect of impact loading on the PDC:

- **Damped power source:** Use of damping ensures that all components move at a controlled velocity, eliminating the impact that would be seen in a spring-driven device.
- **Impaction timing:** The second technique aims to prevent impaction on the PDC at the instant of delivery. Rather than releasing the energy in the power source at the point of activation, the power source is already engaged with delivery components. This provides greater control over component positions and loadings and therefore reduces risk of part failure due to impact.
- **Reduction of activation forces:** Keeping the device activation force low reduces the likelihood of the user exerting undue force onto the device, either by gripping it improperly or by applying it too forcefully onto the injection site. Typically, high pressure requirements necessitate the use of high activation forces. The ability to "decouple" these activation forces from pressure requirements allows minimal user input to deliver highly viscous formulations in a controlled manner.

CONTAINING HIGH PRESSURES

Once delivery variables have been altered to optimise PDC pressure, the next step is to ensure acceptable burst strength of the PDC. An obvious way to do this is through material selection. Glass, which is frequently used for drug containment, is a brittle material and therefore highly susceptible to damage, such as scratches, which can reduce fracture strength. Whilst it is not necessarily any stronger in principle, cyclo-olefin co-polymer (COC) is, in practice, far more robust. Comparatively, COC is a more ductile material than glass, allowing the PDC to deform, flex or fail plastically under high pressures. Glass, however, is susceptible to shatter under significant stress, making it a risky option for use with high viscosity formulations.[15]

The use of COC allows for greater design freedom in the development of PDCs, enabling integration of a wide range of features, which in turn increases the versatility of both components and the mechanism as a whole. The ability to adjust the shape, size and features of the drug container allows optimisation and a suitable safety factor for a 100 bar delivery pressure.

Finite element analysis (FEA) is an extremely powerful tool for assessing the capability of a container design prior

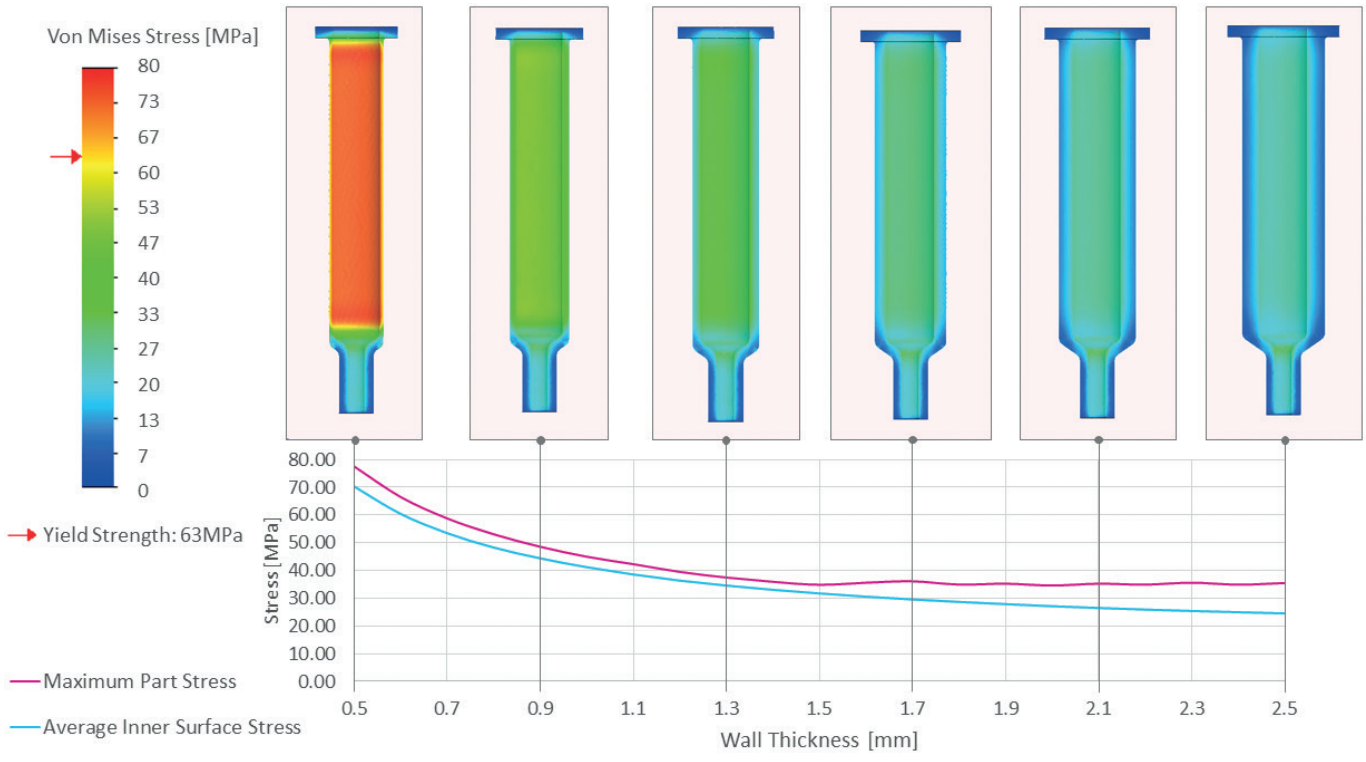

Figure 4: FEA analysis demonstrating wall thickness optimisation of a COC container at 100 bar pressure. Here, a wall thickness greater than 1.5 mm provides minimal benefit to stress reduction within the component.

to design freeze. Examining container design using FEA allows assessment of parameters (e.g. wall thickness or draft angle) which are likely to have the greatest impact on component stress. This understanding allows adjustment and trial of diverse geometries in order to reduce and optimise stress within the container (Figure 4).

ACHIEVING HIGH PRESSURES

Achieving high pressures within the PDC requires a plunger that will operate effectively at such pressures. The plunger must maintain a delicate balance between ensuring low friction within the container whilst preventing any drug backflow behind the seal when pressurised. The plunger should also provide a sterile barrier. This can present a challenge for plunger technologies.

A standard approach to plunger design is to use rubber. Rubber plungers seal effectively, but the friction force between the rubber and container can be notoriously difficult to manage. A range of surface finishes such as silicone oil or plasma treatment have been developed to manage this, with varying degrees of success.[16]

In high pressure environments, the breakout and glide force of rubber can be greatly exacerbated. Due to the compliant nature of rubber, when high pressure is applied the plunger can easily lose its shape, becoming highly compressed and thus producing a very high contact pressure with the glass. As the Poisson's ratio of rubber is very high, any axial force applied quickly becomes a localised radial force, which increases both breakout and glide force, in addition to the risk of container fracture.

To tackle this issue, Oval has developed a high-pressure cup seal design, which overcomes the friction challenges seen in traditional plungers. By decoupling the microbial and liquid seal barrier functions from one another, any conflicting requirements can now be managed separately. The design consists of a reinforced high-density polyethylene (HDPE) component, which provides the liquid seal. This provides a robust sealing surface with the stability to manage high pressures and sufficient lubricity to prevent excess glide forces. Container closure integrity (CCI) within the PDC itself is handled by a separate layer of aluminium foil, induction welded across the rear of the container, acting as a microbial barrier, and is a robust solution for high viscosity delivery. Figure 5 illustrates Oval's high viscosity platform PDC.

Figure 5: Oval's PDC technology optimised for high pressure, high viscosity delivery.

CONCLUSION

The tools and techniques used by Oval help to overcome many of the challenges presented by the delivery of highly viscous formulations. The combination of COC container technology with a thorough drug characterisation programme provides the ability to freely alter drug delivery variables. This allows the effective management of complex and conflicting delivery requirements, ensuring an ability to deliver high pressures in a safe and controllable manner. It is this approach which allows Oval the flexibility to achieve a truly "human" solution to autoinjector design and ensure increased acceptability and compliance for those patients using its devices.

ABOUT THE COMPANY

Oval was set up to develop autoinjectors that meet the needs of patients and a broad range of drugs, including biologics. Current Pharma pipelines include formulations that pose a number of challenges, including those that are fragile and easily degraded, viscous formulations (some of which exhibit non-Newtonian characteristics) and, increasingly, delivery volumes of up to 3 mL. Owning the primary drug container allows integrated devices to be designed. This design freedom enables novel mechanisms to be introduced, smaller devices to be developed and the use of polymeric materials, giving customers complete control over critical component tolerances and control over their supply chain.

The acquisition of Oval by SMC Ltd, a US-based medical device manufacturing company in 2016, has provided access to world-class device manufacturing capabilities in multiple locations in the US and India. Oval/SMC can now provide customers with a complete service, from customisation of subcutaneous and intramuscular platforms, to production of clinical trials devices and commercial scale manufacture. SMC can also offer integration of filled primary drug containers with secondary packaging and distribution if required.

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ABOUT THE AUTHORS

Jonathan Bradshaw is a design engineer with a background in industrial design and a Master's in Medical Device Engineering. Mr Bradshaw has experience in the design, development and commercialisation of fluidic dilution and dosing systems, cardiac catheterisation devices and drug delivery technologies. Currently Mr Bradshaw works as a Device Development Engineer within Oval Medical Technologies where he focuses on furthering the development of the company's novel PDC and autoinjector technology to ensure its devices offer reliability and consistently high performance in combination with usability benefits.

Susanna White has worked as a Mechanical Engineer at Oval Medical Technologies for the past six years, where she is involved in the design and test programmes for Oval's innovative polymeric PDC. Much of her work has focused on the study of highly viscous and non-Newtonian drug formulations – using numerical modelling techniques in combination with experimental investigation in order to achieve the most appropriate delivery system for challenging formulations. Ms White graduated from the University of Cambridge (UK) with a Masters in Engineering for the Life Sciences.