Characterisation & Delivery of Ultra-viscous & non-Newtonian Formulations

James Hance
Senior Device Development Engineer
James.Hance@ovalmedical.com

Oval Medical Technologies
Unit 3, Enterprise 3930
Cambridge Research Park
Beach Drive
Waterbeach
Cambridge
United Kingdom
T: +44 1223 736 220
www.ovalmedical.com

The most recent innovations in injectable formulations are pushing the limit of performance and design of many traditional drug-delivery platforms. We are seeing a significant increase in the number of highly viscous (HV) formulations (100-1000 cP) and ultra high-viscous formulations (UHV) (1,000-100,000+ cP) in the field of Long-acting injectables and biologics. In addition to high-viscosity these formulations often exhibiting non-Newtonian flow characteristics, or in the case of suspensions, 'clogging' characteristics. A vital step in successful and optimal autoinjector device platform development is to gain a solid understanding of these characteristics at the earliest stage. This poster will discuss how Oval goes about this process with the use of the innovative Injection Characterisation System (ICS).

Specifying an Injectable Delivery System

We begin the design process of a device by establishing a target product profile of the product and formulation through early interactions between product developers, formulators and medical experts. Here, key parameters such as the route of delivery, delivered volume and bolus requirements (if there are any) are established. We will usually try to gain an understanding of the patient group with key parameters such as the patient physiology, injection depth, injection site and the injection setting such as a clinical, emergency, home-use, etc. These key factors influence key decisions around the size, complexity and injections rate of the device and establish the focus of the Formulation Characterisation process (Figure 1).

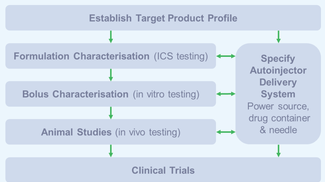


Figure 1: The process of Specifying an injectable delivery

Formulation Characterisation

A key part of Oval's process is to analyse these formulations using the ICS, which allows evaluation of drug flow under a variety of device parameters.

Highly viscous formulations can display a number of challenging delivery behaviors. Many can demonstrate non-Newtonian behaviors, have a high sensitivity to temperature or, in the case of suspensions, have a tendency to clog the needle or settle out of suspension over time. All of these characteristics should be well understood early within the design process as this knowledge is fundamental to the whole delivery system.

Describing Non-Newtonian Fluids

Many high-viscosity formulations exhibit shear-dependant behaviour defined by various models including power law, Carreau and others. Power law fluids, which are the focus here, demonstrate a time-independent log-log relationship between shear stress and viscosity described by:

$$\mu_{eff} = \mu_0 \left(-\frac{du}{dr}\right)^{n-1}$$

Where ***du/dr*** is the flow velocity gradient, ***μ0*** is the flow consistency index which describes the low-shear viscosity and ***n*** is the flow behaviour index. Unlike Newtonian fluids which form a parabolic flow profile in a needle (Figure 2), the flow profile of power law fluids is defined by the expression for flow velocity ***u*** at a given radial location ***r*** :

$$u(r) = \frac{n}{n+1}\left(\frac{dp}{dl}\frac{1}{2\mu_0}\right)^{1/n}\left(R^{\frac{n+1}{n}} - r^{\frac{n+1}{n}}\right)$$

Where ***R*** is the maximum internal radius and ***dp/dl*** is the pressure gradient along the length of the needle. This creates a unique volumetric flow rate ***Q*** at a given pressure (applied force ***F*** and container internal bore ***D***):

$$Q = \frac{\pi d^3}{8\left(\frac{1}{n}+3\right)}\left(\frac{Fd}{\pi D^2 l \mu_0}\right)^{\frac{1}{n}}$$

Where ***d*** is needle internal diameter, and ***l*** is the needle length.

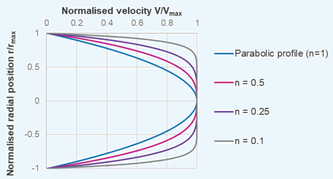


Figure 2: Illustration of a power law fluid velocity profile in a needle depending on the flow behaviour index

Injection Characterisation System

Oval's proprietary Injection Characterisation System (ICS) overcomes issues associated with traditional rheological formulation characterisation by performing it in situ. The set-up of the ICS is like that of an autoinjector, with the addition of a range of instrumentation to provide feedback on the injection process (Figure 3).

It consists of a syringe attached to a needle via a pressure transducer to monitor internal pressure within the syringe. Behind the syringe is a plunger rod connected to a linear encoder, tracking the rate of delivery. This is powered by a spring which acts on a load cell to monitor the force needed for delivery. Combining the outputs of these sensors provides a huge range of information about the formulation (Figure 4).

Apparent formulation viscosity is determined for a wide range of tests (varying needle gauge and length, spring force, etc.) and environmental conditions. Changes in the formulation arising from recipe changes, processing and ageing can also be detected, giving an indication of the impact of batch-to-batch variation or comparing different candidate formulations for injectability.

Closely approximating the delivery system at an early development stage helps detect and mitigate unforeseen risks.

Figure 3: the Injection Characterisation System

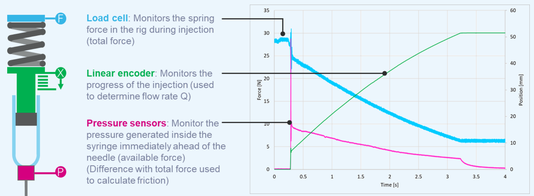


Figure 4: Measurement sensors in the ICS capture data in real-time

Using Drug Characterisation to Define Mathematical Models

The force of springs traditionally used in autoinjectors varies depending on the level of spring compression. The spring force at a certain spring length ***F*** is defined by:

$$F = F_0 - kx$$

Where ***F0*** is the initial force, ***k*** is the spring rate constant and ***x*** is the displacement of the spring in axial expansion. Substituting the spring force relation into the previously defined flow rate equation and integrating over the delivery stroke provides a relation for injection time:

$$Injection\ Time\ (t) = \frac{d^3}{Ck\left(1-\frac{1}{n}\right)}\left[F_0^{\,1-\frac{1}{n}} - (F_0 - Lk)^{1-\frac{1}{n}}\right]$$

$$Where,\ C = \frac{d^3}{2D^2\left(\frac{1}{n}+3\right)}\left(\frac{d}{\pi D^2 l \mu_0}\right)^{1/n}$$

Figure 5: Illustration of power law constants' effect on delivery profile. Assumptions: μ0 = 1000 mPa sn. D = 8.65 mm, l = 20 mm, d = 0.34 mm F0 = 45 N, k = 1.5 N/mm, Fmin = 5 N.

Where ***L*** is the delivery stroke (mm). This allows injection time for a power law fluid to be calculated from the starting force and the delivery stroke (Figure 5).

Application to Monte Carlo Simulations

With injection time represented by a simple mathematical relation, a Monte Carlo simulation of delivery times can be performed (Figure 6). Each input variable is described by an appropriate statistical distribution generated from supplier specifications, predicted process capability or characterisation of device components.

Through random sampling from the input variables, the simulation generates predicted delivery time for millions of simulated devices.

This process allows the impact of needle and spring combinations to be evaluated early in the development process. Verification of the model is done using physical testing of the formulation in the appropriate context (lab-based injection rigs or prototype devices). Power law formulations characterised in the ICS show a high degree of correlation between real and simulated deliveries. Due to confidentiality and the unique behaviour of the formulations, these results cannot be shown.

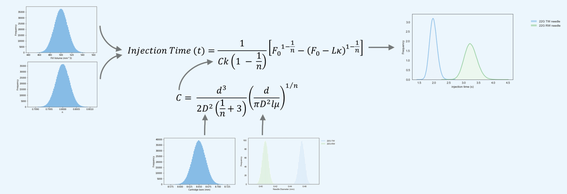


Figure 6: Process of needle optimisation through Monte Carlo simulation of a power law fluid.

The Effect of Viscosity and non-Newtonian Fluids

One aspect of injecting biologics that can be challenging is that they tend to have both relatively higher viscosities than simple molecules and display shear-thinning behaviours.

Newtonian fluids have an inverse relationship between delivery force and delivery time. Therefore small variations in delivery force can result in similar variations in delivery time.

Whereas **Shear-Thinning** fluids become less viscous when under any form of loading. This amplifies the impact that variations in delivery force have on the final delivery time and can lead to very unpredictable deliveries (Figure 7).

This increase in the variability of delivery time is obviously bad for useability and patient satisfaction but can also have more worrying consequences such as **Incomplete / wet injections** occurring as a result of extended injection times. Injections that are significantly faster than nominal have even been seen to **cause tissue damage**. This is visible in images taken from MRI scans, comparing one of a porcine tissue sample that has been injected at a low rate and the other that has been injected at a very high rate (Figure 8).

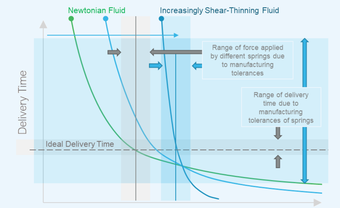
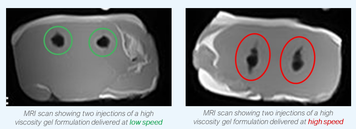


Figure 7: comparison of increasingly shear-thinning fluids (non-Newtonian) as the delivery force is increased

Approaching Autoinjector Design with Dampening

Damping can have a great impact on the injection times of shear-thinning formulations. (Figure 9). The red area represents the predicted delivery times for the formulation delivered with a conventional compression spring accounting for the batch-to-batch variation of the formulation. The blue area calculates the delivery time range assuming a highly damped gas spring is being used. Given a device requirement that injection takes no longer than 10s, damping means that the range of possible delivery times is significantly reduced.



MRI scan showing two injections of a high viscosity gel formulation delivered at low speed

MRI scan showing two injections of a high viscosity gel formulation delivered at high speed

Figure 8: the effect of injection delivery speed

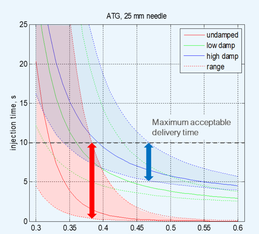


Figure 9: the effects of a dampened system

Oval has worked with a leading European gas strut supplier to develop modified gas springs, which incorporate damping to significantly decouple delivery rate from formulation viscosity. This damping reduces the impact that shear thinning formulations have on delivery time and results in a much more predictable device. Other benefits of damping include reducing the impact load placed on parts during delivery and lessening the 'kickback' experienced by users. Both of these can be significant issues when using the high forces required to inject high viscosity formulations.

The incorporation of this technology in an autoinjector allows for a robust device which optimises injection performance and vastly improves patient comfort.

References:
Vilaplana M, Vasiev A, White S, *"Function-Based Primary Packaging Design for Injecting Viscous Non-Newtonian Formulations"*, *ONdrugDelivery Magazine*, Issue 109 (Oct 2019), pp 20-25.

Guidance for Industry,Container Closure Systems for Packaging, Human Drugs and Biologics",.US FDA, May 1999.

"Fina Cartridges", Company Web Page, Stevanato Group, Sep 2019. (https://pharma.stevanatogroup.com/glass-primary-packaging/products-platforms/cartridges/#fina-cartridges)

"Technology Overview", Company Web Page, SiO2 Medical Products, Sep 2019 (http://www.sio2med.com/technology.html)

"Coating of COC". Company Web Page, Micronit, Sep 2019. (https://www.micronit.com/microfluidics/Coating-of-COC.html)

Forcinio H, "Selecting Primary Packaging for Parenterals". Pharm Tech, 2018, Vol 42(7), pp 46–50.

"SCHOTT TopPac® - Polymer Prefillable Syringes", Company Web Page, Schott, Sep 2019. (https://www.us.schott.com/pharmaceutical_packaging/english/products/syringes/polymer_syringes.html)

"Burst Pressure & Fracture Mechanics of Technical Glass Tubing". Company Web Page, Schott, Sep 2019. (https://www.us.schott.com/tubing/english/products/properties/burst-pressure.html)

Wohlland A, et al, "Encoding and Reading of Codes on Glass Containers for Pharmaceutical and Diagnostic Products." Die Pharmazeutische Industrie, 2009,Vol 71(6), pp 1770-1774.