Drug Characterisation:

A key factor in autoinjector design for more challenging formulations

Susanna White, Oval Medical Technologies

OVAL MEDICAL TECHNOLOGIES

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The most recent innovations in injectable formulations are beginning to push the limits of many traditional drug delivery platforms. Long-acting injectables and biologics make up an increasing proportion of the drugs in development, with potential consequences including viscous formulations, complex fluid properties (e.g. non-Newtonian suspensions and emulsions) and high injection volumes. At Oval Medical Technologies, we approach delivery of these formulations through developing an in depth understanding of their properties, and the unique challenges that they pose at the very earliest stage in the design process. Below we discuss the process used to gain this insight, including examples of their impact on autoinjector design.

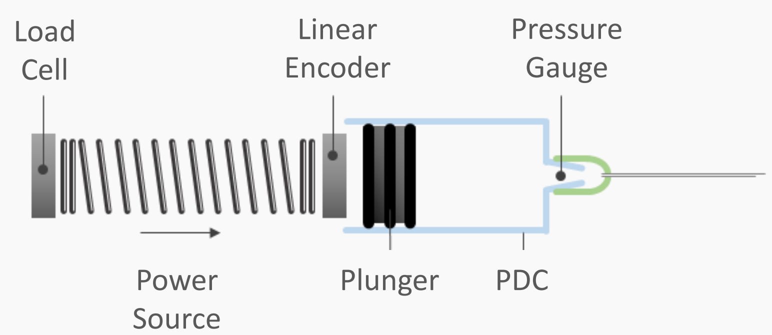
The Injection Characterisation System

Oval Medical Technologies has developed an Injection Characterisation System (ICS) to characterise challenging and unusual fluids. This consists of a modular drug delivery system fitted with sensors allowing feedback on many facets of the injection process at a sampling rate of 25kHz. Delivering at normal injection speeds, this modular system facilitates the testing of different needles, power sources, plungers and containers to determine the effect they have on delivery, whilst allowing the exploration of a wide range of possible delivery configurations.

Three key sensors are distributed throughout the system:

- **Load cell** (blue curve) **:** recording the force during delivery
- **Pressure gauge** (pink curve)**:** measures the pressure within the Primary Drug Container (PDC)
- **Linear encoder** (green curve)**:** tracks plunger position throughout delivery allowing analysis of the delivery speed

Output graphs are used to calculate parameters such as drug viscosity, plunger friction, and to highlight any unexpected characteristics that the formulation may exhibit.



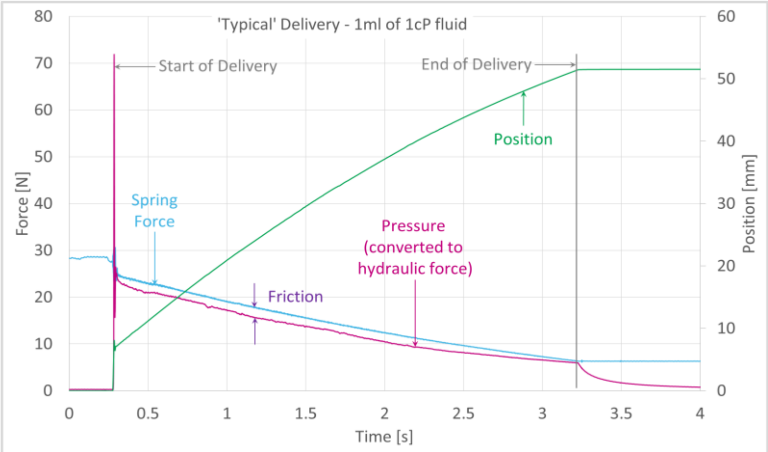
Drug Analysis

This approach allows observation of delivery process characteristics, otherwise unattainable using a standard motorised force gauge. This accurately measures the viscosity in an autoinjector context, including indication of the homogeneity of the fluid, and reveals the influence of a range of variables (shear rate, temperature, age, batch variability etc.) on the fluid. Details informing device design (e.g. the friction of different plungers and how delivery into flesh can alter the delivery profile) can also be analysed.

This data informs a numerical model which allows an optimised delivery system to be selected for the formulation.

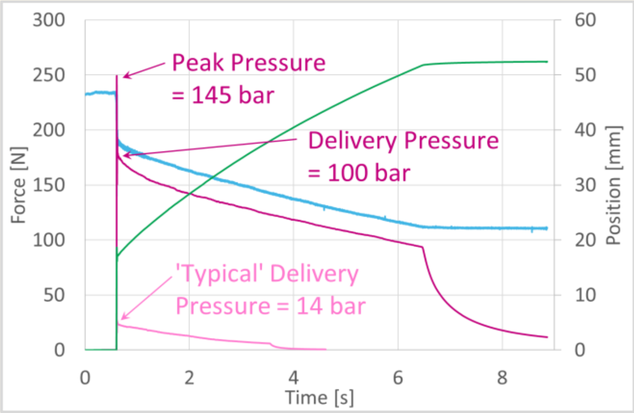
Outcomes for Autoinjector Design

The outcome of this approach is a thorough understanding of the formulation being delivered in the context of the delivery mechanism. This allows accurate specification of the autoinjector parameters (needle gauge, power source etc.) and an informed awareness of the effect of tolerances on device performance (delivery time, device recoil etc.). For many viscous formulations, this testing highlights the requirement for high delivery pressures far beyond those currently achievable with glass syringes. In response to this issue, Oval has developed a polymeric PDC capable of withstanding internal pressures of up to 300bar enabling the delivery of challenging formulations within a user-centric device.



High Volume & Viscosity Drugs

Issues with patient comfort are often observed when delivering a highly viscous and/or of a large volume formulation. Use of a small needle gauge will result in a delivery time that is unsuitably long, whereas an increase in needle gauge will lead to a reduced delivery time with the risk of intensifying discomfort at the injection site. To overcome this, it is necessary to increase the pressure inside the PDC as shown. The inherent strength of glass places a limit on how much the pressure can be increased, however through using polymers with higher strength and lower fragility than current glass technology it is possible to accommodate much greater pressures. Using these pressures vastly increases the viscosity and volumes of fluid that can be comfortably delivered.



Non-Newtonian Fluids

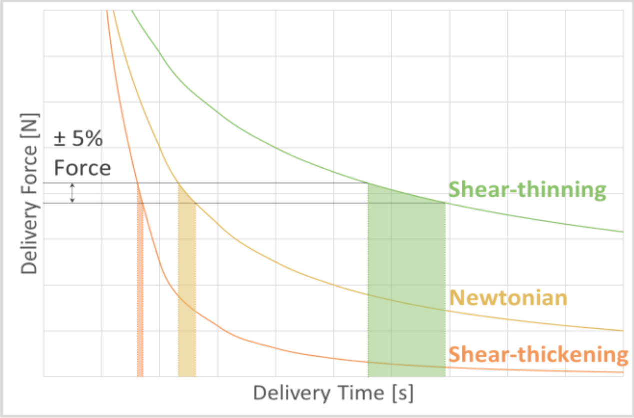
The viscosity of Non–Newtonian fluids varies based on applied stress. Although these can take various forms, the most common types are 'power law' fluids, where the effective viscosity of the fluid is proportional to the shear rate it is experiencing. These can be either shear-thickening or shear-thinning in nature, however shear-thinning (pseudo-plastic) fluids pose the biggest challenge due to their lack of consistency. Small changes in the device (due to tolerances or batch to batch variation) can be amplified by the fluid, leading to considerable changes in delivery time. To mitigate this effect, it may be necessary to include a power source with damping.

Newtonian Fluid

$$\tau = \mu\dot{\gamma}$$

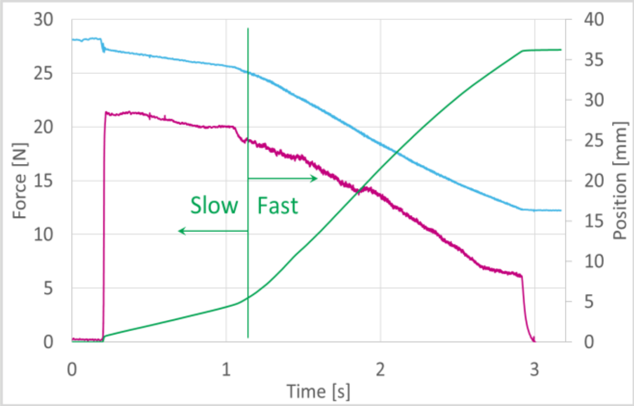
Power Law Fluid

$$\tau = K\dot{\gamma}^n$$



Suspensions

Suspensions are vulnerable to settling during storage. Unless this is addressed (e.g. through device agitation as an additional user step), this will result in a two–phase suspension with two distinct viscosities and a two stage delivery. At the start of delivery the plunger moves slowly as it is delivering settled sediment, however beyond this delivery of the remaining fluid takes place much more quickly. To combat this, an increase in the overall amount of force being used in the device allows the whole system to become less sensitive to this variation in viscosity. This approach is only possible if the PDC is capable of withstanding the pressures required to deliver, giving polymeric PDCs the advantage for this type of delivery.



Emulsions

Emulsions consist of two distinct fluids, each with a different viscosity. This causes oscillation of the plunger movement over the course of delivery, leading to a stepped motion and fluctuating load profile. The extent of these oscillations is determined by the size of the dispersed fluid particles and the stability of the emulsion. The resulting delivery can be very 'start-stop' and could be unsettling to the user.

This understanding allows an appreciation of the effect to the user and an opportunity to better manage this through system design. For example, Oval's polymeric PDC can manage increased injection forces thus mitigating the effect of these fluctuations on the patient.