High Viscosity Formulations: Developing a ‘Human Solution’ to Autoinjector Design

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Within the injectable drug landscape, the availability and use of High Viscosity (HV) formulations is growing, often driven by developments such as Long-Acting Injectables (LAI) technologies. Typically, LAI products consist of formulations that are highly viscous in nature (1000–1,000,000cP) which can present a range of delivery challenges such as non-Newtonian flow, or in the case of suspensions, ‘clogging’ characteristics. Often, these characteristics are well beyond the normal limits of injection devices and can present many difficulties for Subcutaneous (SQ) and Intramuscular (IM) drug delivery. When delivering High Viscosity formulations, there is a greater trade-off between achieving satisfactory delivery and acceptance to the patient. However, these requirements often conflict. To create a truly ‘Human Solution’ when delivering HV formulations, a suitable balance between the two must be achieved. This paper discusses the importance of achieving a ‘Human Solution’ to HV autoinjector design.

Conflicting Requirements

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 a HV delivery can be achieved, e.g. through increasing injection delivery times and larger spring forces. However, all these approaches risk reducing patient acceptability due to an increase in pain, and a compromised user interface (e.g. a large and noisy device). This conflict often presents many challenges to traditional device design approaches which are restricted in their possibilities and are less able to manage these opposing requirements.

Delivering Highly Viscous Formulations

To achieve HV delivery which is within the capability of the device mechanism, device developers can manipulate the following four parameters:

Drug Viscosity
Drug Volume
Needle Gauge
Delivery Time

These variables are key in determining the ability of the device to deliver highly viscous drugs and are crucial to delivering the formulation on the user. However altering delivery variables should be approached with caution as it is imperative to understand the potential impact on the injectable process itself. This is particularly crucial when considering the introduction of insoluble bolus formulation characteristics. For LAIs in particular, the surface area of the particle is one of the most crucial factors. Consistent bolus formation is key in achieving the desired pharmacokinetic profile and therefore therapeutic effect.

The main factor affected by these variables is internal container pressure, which is produced by the power source acting on the plunger. Using a modified form of the Hagen-Poiseuille equation, the internal pressure the internal pressure necessary to deliver a given drug formulation can be calculated (Equation 1):

\[ P = \frac{8 \mu L}{r^4} \]

Where:
- \( P \) = Drug Pressure
- \( L \) = Needle Length
- \( \mu \) = Viscosity
- \( d \) = Internal Needle Diameter
- \( V \) = Volume

To the balance, formulation and patient requirements, Oval Medical Technologies has developed an ‘Ideal’ patient-oriented specification which forms a lightweight framework for maximising patient acceptability of HV autoinjectors:

- 3–5 Second Delivery Time
- 23G Needle (IF), 25G needle (SQ)
- 3ml Maximum Volume
- 1000cP Maximum Viscosity

An Optimal Drug Delivery Specification for the Patient

Freed from altering delivery variables risks negatively influencing the acceptability of a device to a patient. To account for this, Oval Medical Technologies first define a delivery specification which maximises acceptability to the patient, and then develop this into a solution which also caters to the challenging nature of the drug. This approach requires an appreciation of the relationship between patient requirements and drug deliverability variables, as broadly defined in Figure 1.

The following parameters have a direct impact on patient experience, and therefore can influence the acceptability of a device:

Needle Gauge: Needle width can have an impact on the perceived pain of injection4,6. Reducing needle width can reduce pain and increase patient acceptance. However, there often exists a trade-off between minimising injection pain and other common issues such as clogging or achieving the required needle strength. It is important to balance adequate needle strength for the application with pain perception and the required flow rate for HV drugs1,8

Delivery Time: HV drugs, flow rate and therefore delivery time is key in ensuring adequate depot/bolus formation13. Shorter injection times (<1 sec) can risk jetting and be difficult to deliver both SQ and IM, whereas longer injection times (>30 sec) can negatively impact patient acceptance. Although flow rate can have varying impact on perceived pain14, there is a need to define a longer injection times that longer injection times can prolong formation from needle insertion itself thus reducing patient acceptability15. Ultimately a delivery time acceptable for both bolus formation and patient tolerability is desirable.

Volume: Typically, LAIs range in volume from 1ml-3ml, with lower volume injections being generally better tolerated in SQ applications16. With volume being linked to viscosity, interestingly there are indications that higher viscosity products can improve pain perception17; however this is likely dependent on other variables such as active ingredients, pH and temperature.

Approaching Autoinjector Design

To achieve a patient-oriented delivery specification whilst overcoming the challenging nature of the formulation, an increase in delivery pressure is required. For HV formulations, this increase in internal POC pressure is of clear benefit to the patient (Figure 3).

Analysis has shown that delivering 1ml of a 1000cP formulation through a 25G needle over 5 seconds, can require an internal POC pressure of 3000psi to achieve. Considering common issues imperative that the device mechanism can deliver the forces required to achieve these pressures in a safe and practical manner.

These requirements have implications for traditional glass-based autoinjector designs due to the brittle nature of glass, its high susceptibility to damage such as scratches, and the resulting reduction in fracture strength. It is not necessarily any stronger in principle, Cyclic Olefin Copolymer (COC) is far more robust and offers greater flexibility to packaging and management of delivery release forces. Comparatively COC is a much durece material than glass, allowing the device to function over a much wider range of pressures.

Oval Medical Technologies’ approach ensures HV drug formulations are fully characterised and where appropriate utilise the benefits of COC to ensure an optimal drug delivery system. This allows the effective management of complex and conflicting delivery requirements and ensures an ability to deliver high pressures in a safe and practical manner. It is this approach which allows Oval the flexibility to achieve a truly ‘human solution’ to autoinjector design and promote increased acceptability and compliance for those patients using its devices.