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 Injectable (LAI) technologies. Typically, LAI products consist of formulations that are highly viscous in nature (100cP – 1,000cP) 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 HV formulations, there exists a delicate balance between achieving safe delivery of the drug and doing so in a way which is practical and acceptable 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 poster 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 larger needle diameters, longer 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 autoinjector 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 in defining the likely effect of the injection process on the user. However altering delivery variables should be approached with caution as it is imperative that they are tuned to produce consistent bolus characteristics. For LAI's in particular, the surface area of the bolus formed on injection is critical - consistent bolus formation is key in achieving the desired pharmacokinetic profile and therefore therapeutic effect[1].

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):

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

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

Equation 1:
Modified Hagen-Poiseuille Equation[2]

An Optimal Drug Delivery Specification for the Patient

Freely 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 appreciation of the relationship between patient requirements and drug delivery 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 injection[3,4]. Reducing needle width can reduce pain and increase patient acceptance. However, there often exists a trade-off between minimising injection pain and overcoming 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 drugs[4,5,6] .

Delivery Time: With HV drugs, flow rate and therefore delivery time is key in ensuring adequate depot/bolus formation[5]. 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[7,8], there are indications that longer injection times can prolong pain from needle insertion itself thus reducing patient acceptance[8,9,10]. 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 applications[7,11,12]. With volume being linked to viscosity, interestingly there are indications that higher viscosity products can improve pain perception[9], however this is likely dependant on other variables such as active ingredients, pH and temperature.

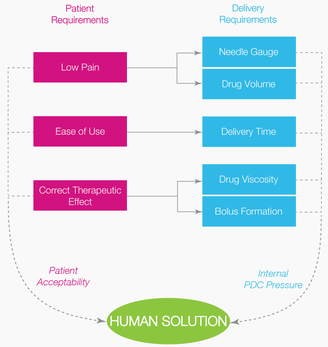

Figure 1: To maximise patient benefit, delivery variables must be influenced by a patient-orientated specification.

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

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

The Importance of Formulation Characterisation

When developing an autoinjector mechanism that can meet the 'ideal' patient delivery specification, it is imperative to understand the flow characteristics of the formulation. Through implementing a full drug characterisation programme early within the device development process, any difficult or non-desirable delivery characteristics will be quickly revealed. This provides device developers the understanding necessary to manipulate delivery variables effectively, resulting in a device which is considerate of both patient and formulation requirements.

Commonly, drug products can present a multitude of delivery characteristics. HV products such as LAIs are formulated to provide a specific therapeutic effect that is supported over monthly, bimonthly, and in some cases, three-monthly dosing regimens[13] . 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 (Figure 2) ;

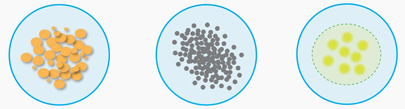

Figure 2: Key approaches to developing slow release formulations[1]

These approaches or 'vehicles' are typically of high molecular weight, which in turn increase the viscosity of the entire formulation. This can also lead to non-Newtonian behaviour and an increased sensitivity to environmental conditions. Delivering these via autoinjector can be further complicated by other characteristics such as clogging and in the case of suspensions, settlement during storage.. This puts great onus on the delivery mechanism to overcome or manage the delivery requirements of a formulation.

Approaching Autoinjector Design

To achieve a patient-orientated delivery specification whilst overcoming the challenging nature of a formulation, an increase in delivery pressure is required. For HV formulations, this increase in internal PDC 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 PDC pressure of ~100bar. As such it is 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. Whilst it is not necessarily any stronger in principle, Cyclic Olefin Copolymer (COC) is far more robust and offers greater design freedoms to manage delivery pressures and forces. Comparatively COC is a more ductile material than glass, allowing the PDC to deform, flex or fail plastically under high 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 controllable 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.

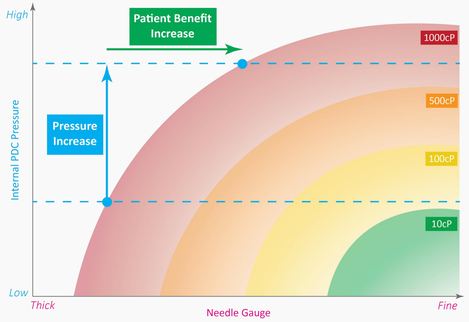

Figure 3: Increasing the pressure loading within the PDC allows for improved patient benefit through use of finer needle gauges at fixed viscosities.

References:

1. A. A. Sheikh, S. R. Sheikh, and Z. Zaheer, "Injectable Controlled Release Drug Delivery Systems," Asian Journal of Pharmaceutics, vol. 10, no. 4, pp. 464-471, 2016.
2. S. Sutera and R. Skalak, "The History of Poiseuille's Law," Annual Review of Fluid Mechanics, vol. 25, pp. 1-19, 1993.
3. L. Arendt-Nielsen, "Pain following controlled cutaneous insertion of needles with different diameters," Somatosensory & Motor Research, vol. 23, no. 3-2, pp. 37-43, 2006.
4. P. V. Beirne, S. Hennessy, S. L. Cadogan, F. Shiely, T. Fitzgerald, and F. MacLeod, "Needle size for vaccination procedures in children and adolescents," Cochrane Database of Systematic Reviews, no. 8, pp. 1-121, 2018.
5. S. P. Schwendeman, R. B. Shah, B. A. Bailey, and A. S. Schwendeman, "Injectable controlled release depots for large molecules," J Control Release, vol. 190, pp. 240-253, 2014.
6. S. Buchholz, Henke's Med-Math: Dosage Calculation, Preparation & Administration. Philadelphia: Wolters Kluwer Health | Lippincott Williams & Wilkins., 2012.
7. T. Heise et al., "Impact of injection speed and volume on perceived pain during subcutaneous injections into the abdomen and thigh: a single-centre, randomized controlled trial," (in eng), Diabetes Obes Metab, vol. 16, no. 10, pp. 971-6, Oct 2014.
8. L. F. Tangen et al., "The influence of injection speed on pain during injection of local anaesthetic," (in eng), J Plast Surg Hand Surg, vol. 50, no. 1, pp. 7-9, 2016.
9. C. Berteau, O. Filipe-Santos, T. Wang, H. E. Rojas, C. Granger, and F. Schwarzenbach, "Evaluation of the impact of viscosity, injection volume, and injection flow rate on subcutaneous injection tolerance," (in eng), Med Devices (Auckl), vol. 8, pp. 473-84, 2015.
10. G. S. Harvinder and M. R. Prausnitz, "Does Needle Size Matter?," J Diabetes Sci Technol., vol. 1, no. 5, pp. 725-729, 2007.
11. J. T. Jorgensen, J. Romsing, M. Rasmussen, J. Moller-Sonnergaard, L. Vang, and L. Musaeus, "Pain assessment of subcutaneous injections," (in eng), Ann Pharmacother, vol. 30, no. 7-8, pp. 729-32, Jul-Aug 1996.
12. C. Berteau et al., "Evaluation of performance, safety, subject acceptance, and compliance of a disposable autoinjector for subcutaneous injections in healthy volunteers," (in eng), Patient Prefer Adherence, vol. 4, pp. 379-88, Oct 5 2010.
13. J. Haste, "Guidelines for the Administration of Long Acting Antipsychotic Injections in Adults," Accessed on: January Available: https://www.sussexpartnership.nhs.uk/sites/default/files/documents/laai_guidelines_-_v5_-_0118.pdf