High Viscosity Formulations:

Developing an Effective Primary Drug Container System

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The past few years have seen a significant increase in the number of high viscosity (HV) formulations (100 – 1000 cP) being developed. Innovations in the field of biologics, as well as an increased interest in the use of Long Acting Injectables (LAIs), mean that autoinjector developers are constantly being challenged by new formulations with increasingly complex flow behaviours. These new formulations can provide a great number of benefits for patients and health care providers through access to cutting edge therapies and by reducing both dosing frequency and delivered volume. However unless they can be delivered in a patient-orientated manner, these benefits cannot be fully realised. There are a number of steps that autoinjector developers can take to meet the challenges posed by such formulations. This poster will focus on some of the techniques that Oval Medical Technologies has used to develop the ArQ™-Bios high viscosity platform (Figure 1).

Traditional Autoinjectors

Many autoinjectors currently on the market consist of a standard glass syringe skinned with a mechanism that manages needle insertion, drug delivery, and needle safety. There are plenty of benefits to this approach; the combination of glass with a rubber plunger is highly impermeable increasing drug stability, and also there is a long history of glass use making it attractive to both manufacturers and regulators.

In order to overcome the challenges presented by HV formulations, it can be necessary to explore the use of new technologies. The use of Cyclic-Olyfin Copolymer (COC) makes it possible to circumvent key known issues inherent in glass syringes. The design flexibility unlocked by this change in material allows the consideration of numerous approaches to autoinjector design. A few of these design possibilities are presented here with discussion of the benefits they can bring to the delivery of HV formulations.

Figure 1: The ArQ™-Bios. Oval's high viscosity platform

Formulation Characterisation

HV formulations can display a number of challenging delivery behaviours. Many can demonstrate non-Newtonian behaviours, 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 delivery system as a whole. A key part of Oval's process is to analyse these formulations using our Injection Characterisation System which allows evaluation of drug flow under a variety of device parameters.

References:
1. Murray H, Froio R, "Assessing Flange Strength and Dimensional Variability. Comparisons of Plastic and Glass 1-mL Long Syringe Systems". BioProcess International, 2014, Vol 12(3), pp 66–69.
2. Reuter B, Petersen C, "Syringe Siliconization: Trends, methods, analysis procedures". TechnoPharm, 2012, Vol 2(4), pp 238–244.

Controlling Force and Impact

Although there are several techniques that can be used to allow delivery of HV formulations such as widening the needle bore or increasing the time to deliver, all have their own repercussions for the usability and comfort of the device. The only approach to accommodate the delivery of high viscosities whilst maintaining a truly patient-centric device is to increase the force applied to the internal mechanism to deliver the drug and to ensure that the force remains isolated from the user.

Increasing the outputs of the power source does however introduce various complications by increasing the energy stored in a device, causing high stresses to build up in its components. In this context, the use of a spring can be sub-optimal. Springs can store a lot of energy and, if they are inadequately constrained in a device, they can build up considerable momentum under free travel causing an abrupt impact on those components in its load path. The effect of this is shown below (Figure 2) as the measured internal pressure within a container reveals a disproportionate peak at the start of delivery when it is impacted by the spring. This can often be the limiting factor for the strength of autoinjector components. Through improved management of the power source, it is possible to reduce the stress inflicted on those components.

Utilising a damped power source rather than a spring is one way to control the forces inside an autoinjector. This prevents the build up of momentum thereby avoiding impact loads which can further stress critical components.

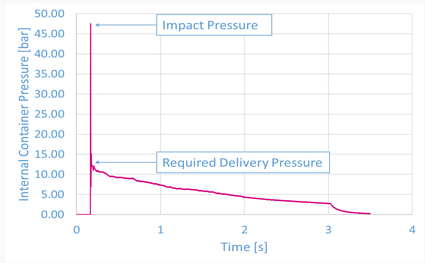

Figure 2: Internal pressure within a container during drug delivery

Another means of lowering component stress within an autoinjector is to limit those external forces introduced by the user. If a device is difficult to operate or requires high activation forces it becomes more likely that the user will impose additional forces on the device either by gripping it too tightly or by striking the injection area with too much vigour. It therefore follows that reducing the activation force of the device will help reduce stresses within it. It can, however, be difficult to decouple the high delivery forces needed for viscous drugs from the low activation forces desired. Oval have developed an activation mechanism which can overcome this issue within its ArQ™-Bios HV platform.

A High Strength Drug Container

Whilst steps can be taken to reduce impacts and unintentional stresses in a device, high pressures are required to deliver highly viscous formulations in a reasonable delivery time and an appropriate needle to the patient. Our development work has shown that it requires ~100 bar to deliver 1ml of a 1,000cP fluid through a 25G needle in 5s. With this in mind, developing a drug container which can withstand these pressures presents further design challenges.

Using COC container material can simplify this task as its properties lend itself to use with high pressures when compared to glass[1]. Glass is a highly brittle material and can be susceptible to damage such as scratches, which can reduce fracture strength. COC is not necessarily any stronger in principle, but it is far more robust. Due to the ductility of COC it is more liable to deform, flex or fail plastically when stressed, whereas glass has a tendency to fracture under high pressures. This shattering produces sharp fragments which pose a significant risk to the patient.

An additional benefit of COC is increased moldability, which affords developers much greater design freedoms. This allows the integration of a wide range of features into the component. These facilitate interfaces with surrounding mechanisms and ensures that the overall design is more compact, more stable and more robust. Design flexibility also applies to parameters such as the shape and size of the container which can be optimised for specific pressures and formulation volumes, as shown in figure 3.

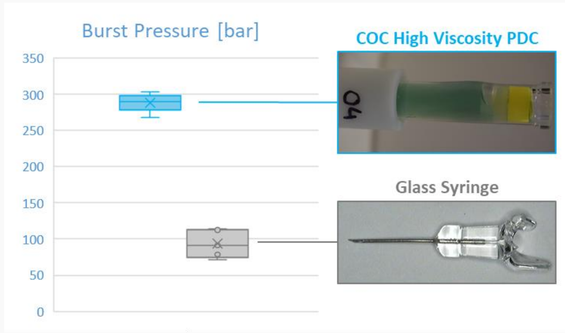

Figure 3: Burst strength of our HV primary drug container (PDC)

A High Pressure Piston

Achieving high pressures during delivery also requires the design of a plunger that can function effectively at pressure extremes. The plunger must maintain a delicate balance between ensuring low friction within the container, preventing drug backflow, and providing a sterile barrier. Combining all of these functions into a single component can be an extremely challenging task. Oval Medical Technologies manage these often conflicting requirements through use of multiple components, as seen in Figure 4.

Figure 4: Oval's HV PDC

Typically, for low viscosity applications, rubber plungers are used in conjunction with glass syringes as they form a reliable seal, however the friction between these two materials can be excessive. There are several means of resolving this, for example component siliconisation processes which are now standard practices within the industry. However, these can give variable results and at high pressures glide force can become an increasing issue[2]. Whilst helpful in forming a seal, the compliant nature of rubber causes the plunger to lose shape entirely under extreme loading. Further the high Poisson's ratio of rubber converts any axial force into a localised radial force on the glass syringe. The result of these two processes are heightened breakout and glide forces and, in severe circumstances, the risk of container fracture.

Oval utilise cup seal and foil technology to address the conflicting requirements that must be managed by a plunger. A layer of aluminium foil is induction welded across the back of the container thus providing a robust microbial seal. The high density polyethylene cup seal then handles the liquid seal whilst its lubricity maintains low glide forces throughout its shelf life. To handle high pressures present during use, Oval have reinforced the cup seal design to ensure stability and rigidity of the component during use.

The Significance for Autoinjectors

Using the development techniques noted within this poster, Oval have created the ArQ™-Bios platform; a high viscosity delivery system which can deliver 1ml formulations up to 1000cP through a 25G needle in <5s, whilst still being user-friendly and unintimidating (figure 5). The use of COC is key as this unlocks design freedoms not available with traditional glass-based systems. This allows the flexibility to truly optimise all aspects of the mechanism.

Through facilitating the delivery of these highly viscous and non-Newtonian formulations Oval endeavour to allow formulators greater freedoms to create drugs with increased therapeutic effect, ultimately resulting in improved treatments for patients.

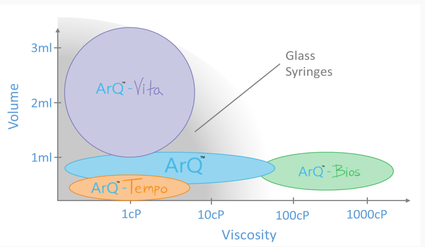

Figure 5: The design space of Oval's technology compared to glass equivalents