INTRODUCTION

Drug development pipelines are showing an increasing trend towards increasing numbers of injectable products, and amongst these an ever larger proportion are viscous biologics and sustained-release formulations. Set against this backdrop, Susanna White, Mechanical Engineer, Oval Medical Technologies, and Louisa Harvey, Director, Harvey Medical, and Consultant to Oval, provide an overview of some of the considerations and challenges faced when designing delivery systems for viscous formulations, and describes Oval’s unique high-viscosity drug delivery device platform.

SUSTAINED-RELEASE FORMULATIONS

Many sustained-release injectable formulations are being developed, as part of life-cycle management strategies, to reduce dosing frequency, and to increase the barriers to entry for generic competition. Sustained-release formulations can have very high viscosities (up to 250,000 cPs), which are extremely difficult to inject manually, owing to the high injection forces required, and cannot be delivered by conventional auto-injectors.

Sustained-release formulations commonly work by forming a bolus of drug within the subcutaneous or muscular tissues, which slowly release drug over time. High-viscosity formulations are required to prevent the drug from dissipating into the bloodstream where it has rapid bioavailability and the sustained-release functionality is lost. It is important that these formulations are delivered to the right area of the body, and that the form of the drug bolus is maintained. If for instance the drug bolus is significantly spread out within the tissue it will have a much larger surface area, which can result in an...
initial spike in drug availability followed by too little in later stages of the dose duration.

Various methods are used to achieve sustained release, and all of these methods are invaluable in enabling a patient to take their chronic medication less frequently. However, there is a significant trade-off between frequency of delivery, and the ability to deliver viscous formulations.

Important issues for consideration when specifying drug delivery devices for viscous formulations include:

- Human factors such as physical usability, patient pain and emotional discomfort
- Mechanical reliability and consistency of performance.

In order to deliver viscous injectables, a fundamentally different approach to the design of auto-injectors is required. Oval Medical Technologies has considered each one of these issues, and has developed a new approach to the design of auto-injectors that brings benefits to the patient, the pharmaceutical company and healthcare providers.

MEETING THE CHALLENGES FOR VISCOS DRUGS

Usability, Patient Preference & Compliance

Pharmaceutical companies and healthcare providers are concerned with patient compliance for obvious reasons, and compliance can be heavily influenced by usability (ability for the user to use the device) and preference (a desire by the user to use a device). Most patients when required to practice self-injection can use a manual syringe to inject an orange, but needle phobias, or the fear of pain, may prevent the same person from injecting themselves for real.

Highly viscous drugs can be particularly painful to inject as the needle diameters are often larger and injection times longer. Ideally the user interface of a device should be designed for the target population. By considering the needs and preferences of the patient, from the beginning, products are much more likely to succeed in the market than devices that are not intuitive to use and do not address specific user preferences such as needle phobias.

High syringe plunger forces may make the injection very uncomfortable for the patient or even be too high for manual injection altogether. Forces can be reduced by using a larger diameter needle but this can be unacceptable to patients, particularly if the needle is visible, and can cause bleeding and bruising at the injection site. The limit of comfortable force for manual injection depends on factors such as the user, the delivery device and the injection site. According to the WHO the maximum force requirement for delivery should not exceed 30 N, but based on Oval’s previous experience, a comfortable limit to enable those with limited dexterity to operate a syringe can be as low as 20 N (4.5lbf).

As an example, 1mL of a 90cPs formulation administered through a 27 G needle can require more than 70 N to deliver, when using a “1 mL Long” manual prefilled syringe. A reasonable size autoinjector based on Oval’s technology can provide 400N (90lbf) allowing small needles to be used. Auto-injectors are therefore the delivery system of choice for highly viscous formulations.

Reliability & Variability

Viscous formulations pose the greatest challenge to the delivery device designer in terms of reliability.

There are numerous issues that make conventional auto-injectors, which include a 1 mL glass syringe, unsuitable for use with viscous formulations. These include:

- tendency of glass to break under high injection forces
- variation in glide forces owing to incomplete siliconisation of glass and the propensity of rubber to stick
- propensity of rubber plungers to leak under high pressures.

For non-Newtonian formulations, small variations in injection force from device to device can lead to very wide variations in injection time.

Plunger stiction in auto-injectors has caused significant problems for the pharmaceutical industry. A number of devices have been subject to batch recalls. For example, in 2006 the Neulasta® SureClick™ auto-injector was recalled for failing to dispense the proper dosage due to sticking plungers. The product was subsequently withdrawn from the market in an auto-injector.

Another related failure mode is juddering of the plunger during delivery, which can cause the user to remove the device before the entire dose has been dispensed.

Opportunities for Delivering High-Viscosity Formulations

Better Syringes

The difficulty in the application of conventional auto-injectors for viscous formulations is resulting in a number of companies choosing prefilled syringes as the delivery device of choice. However users including patients can have difficulty producing high actuation forces, resulting in very lengthy and variable delivery times, use of larger needle diameters, and greater pain and discomfort.

Dilute the Formulation

While many sustained-release formulations require viscosity to function, biologics can be diluted. However, there are limits to the rate at which large volumes of injected drug can be absorbed by the body, so infusion (with associated costs and inconvenience) may be required.

Patch pumps (such as the micro infuser from BD and the SmartDose® from West) allow slow delivery of higher volumes in a home environment and offer an alternative to infusion, but can be costly and less convenient than auto-injectors, and are limited in the volumes that they can deliver compared with infusion.

Use a Larger Needle

Changes to the needle bore have a big impact on the force needed to deliver a drug. However large needles have certain disadvantages:

- They can increase needle phobia
- They can cause trauma at the injection site, including bleeding and bruising
- The drug can escape by flowing out of the hole left at the injection site.

Smaller needles require much higher pressure to administer the drug, which has an impact on usability and comfort for the patient. The injection will inevitably take longer, and the carer may not be able to keep the needle as steady.

There are cases where 18 G needles are used where no alternative options for
delivering high viscosity product are available. However increased market and regulatory pressure to address device usability issues make the use of large needle bores unacceptable since they are painful and can cause large puncture wounds.

Use a Self-Powered Delivery Device

These can offer significant opportunities, and fall into two main categories:

Auto-injectors:

Auto-injectors can provide much higher delivery forces than those achievable by use of a manual syringe. This allows smaller needles, quicker delivery and potentially a much less disconcerting delivery experience for the patient. They can also make self-injection by patients much easier.

Patch pumps:

Patch pumps are suitable for the delivery of viscous biological drugs. They work by delivering the drug slowly, for example over a period of 20 minutes. The main advantage of pumps is their ability to hold larger volumes. The maximum volume that can be delivered subcutaneously using a syringe/auto-injector is dependent on many factors (injection site, depth, speed, absorption rate, level of acceptable pain etc) but is considered by some to be typically around 1.5 mL.6

Pumps are useful for biologics which should be delivered evenly into the blood stream. However, pumps may not work for those drugs with a sustained-release profile because you will not achieve the bolus form that is often needed. An auto-injector is therefore more appropriate for sustained-release formulations.

OVAL’S VISCOUS DRUG DELIVERY PLATFORM

Oval has developed a unique auto-injector platform technology capable of handling highly viscous drugs. It is fundamentally unique and has been shown to be capable of delivering a variety of 1000 cPs solutions (the thickness of motor oil) through a 25 G thin wall needle, in less than seven seconds, using a high viscosity primary drug container. Oval has a technology that has successfully delivered a 250,000 cP non-Newtonian formulation which gave equivalent results to a manual injection in a pharmacokinetic study in dogs.

Oval’s design philosophy is to address Human Factors, device mechanical reliability and consistency of performance to produce devices that are best in class. Glass and rubber are not used in Oval’s high viscosity devices; the primary drug container is cyclic olefin that has been shown to have very high burst strength. The use of a polyethylene cup seal that pushes out the drug during delivery, reduces the risk of leakage under the high injection forces that are required.

The spring force is optimised for a given formulation viscosity and volume, the needle diameter and length and the target delivery time. Oval has developed methodologies to optimise these parameters and works with pharmaceutical companies to provide auto-injectors designed specifically for the target patient population.

Non-Newtonian viscosity

The definition of viscosity was quantified by Newton who realised that for some fluids the rate of flow (γ) was directly related to the applied stress (σ): the constant of proportionality is the coefficient of viscosity (η). Fluids that work to this equation are described as Newtonian fluids, and those which do not are described as non-Newtonian.7 Many highly viscous formulations are also non-Newtonian in character, and these can lead to specific issues around drug delivery (see Figure 2). Oval has direct experience of delivering highly non-Newtonian fluid formulations, and has developed specific delivery technology and test methods to optimise the performance of devices intended to be used to deliver these formulations.

In order to model the behaviour of non-Newtonian drugs, Oval uses a power law relationship between shear stress and shear rate known as the Ostwald–de Waele relationship. This is shown in equation 1 below where K and n are both physical properties of the fluid in question.

1) \[ \tau = K \left( \frac{\dot{\gamma}}{\eta} \right)^n \]

In the case of a Newtonian fluid n would be equal to 1 and K would be the viscosity. Using this model, the relation between pressure drop and flow through a circular tube is given by equation 2.

2) \[ Q = \frac{n \pi^3}{p^3} \left( \frac{\Delta p}{r^2} \right)^{1/n} \]

Here Q is the volume flow rate, \( \Delta p \) is the pressure difference and L and r are the length and radius of the tube respectively. This equation must be simplified, reordered and have logarithms taken to turn it into a form that can be compared to experimental results.

3) \[ \log \left( \frac{\Delta p \cdot r}{L} \right) = n \log \left( \frac{Q}{\pi^3} \right) + \log \left( 2K \left( \frac{1}{\eta} + \frac{2n}{\pi^2} \right) \right) \]

The experimental method involves using a force gauge to push the drug out of a container.
through a needle of known length and diameter at a number of different velocities. These force and velocity data are used to calculate the pressure drop and volume flow rate through the needle, which is then analysed graphically and compared with equation 3 to determine the physical properties, K and n, of the drug.

The same tests are run on the drug whilst it is heated (40°C) and cooled (5°C) to understand its temperature dependency. This is important as, if a drug’s physical properties are highly sensitive to temperature; this may result in an extremely variable delivery time if left unaccounted for in the design, and many biologics are stored at 4°C.

Once the parameters of the drug have been established its behaviour can be predicted, and it is possible to calculate appropriate spring forces required to deliver it. The parameters K and n and equation 2 are then used to determine the force required to optimise delivery time and needle gauge. From this, the most appropriate delivery method can be decided upon.

In some cases the non-Newtonian performance of a formulation can render it unsuitable for conventional auto-injectors altogether. Small changes in spring forces or viscosity due to manufacturing tolerances or temperature etc can have a very significant impact on delivery time, so that one injection may take tens or even hundreds of times longer than another of the same product.

This effect is explained in Figure 2. The two curves show the relative delivery time for different delivery forces of Newtonian and non-Newtonian formulations. Oval has resolved this issue through use of a novel power mechanism which helps to control the rate of drug delivery.

Material selection

As stated earlier, Oval decided to move away from a glass primary drug container to achieve a much higher burst strength, and after careful consideration chose Topas® cyclic olefin copolymer (COC) for their primary drug container. Cyclic olefin is a well-characterised material, used to produce many syringes around the globe. Topas® COC has been in production since 2000. COC was chosen due to its good leachable performance, very high water vapour barrier, excellent chemical resistance, its compatibility with various sterilising processes, and excellent optical properties.

Oval took a revolutionary approach to eliminate rubber, which is traditionally used in glass syringes to create the plunger. Rubber has a propensity to stick to glass and requires lubrication with the silicone oil. Silicone oil can degrade biologics and can act as an adjuvant with some products, which could potentiate an immune response. Rubber plungers have two distinct roles in a glass syringe namely to form the liquid seal of the primary drug container and to push the drug out at point of administration. This design is a compromise since the choice of rubber is not optimal for both functions. High injection forces required for viscous formulations, cause rubber plungers to leak. Oval’s major innovation is the choice of polyethylene cup seal and foil (see Figure 3). The two functions have been split between the polyethylene cup seal (for delivery) and the aluminium foil laminate seal (for container closure integrity). These materials are commonly used for similar functions in many other products. For instance, some dry-powder inhalation devices use aluminium foil to seal the primary container, and many products such as spray cleaner use polyethylene cup seals. Oval has brought these commonly used materials together to resolve the issues with rubber plungers in glass syringes.

In the same way that we viewed the rubber plunger as fulfilling a dual role, thus representing a compromise, the spring in an auto-injector can also be viewed as having two distinct functions. Both concern powering the device but one is to provide the power for the needle to pierce the skin and the other is to drive the plunger and deliver the drug. So, the Oval device uses a two-spring system to actuate the device; the first spring uses a lower force appropriate for piercing the skin. This then activates a stronger spring to provide the force required to deliver the drug. Figure 4 shows the spring force in the Oval device compared with conventional systems.

Customisation

Oval has the ability to customise many aspects of its device, enabling flexibility to build better auto-injector mechanisms. For example, the primary drug container wall thickness can be tailored to make it stronger. Features can be inserted to support the primary drug container. The power source can be modified in accordance with the viscosity. For generating the highest forces, with the most viscous drugs,
Oval has developed safe and reliable power systems that are extremely compact. Where a more expensive power source is required technologies that allow for reuse are available. For example, the power pack can be retained for the next dose with the rest of the device being single-use.

CONCLUSION

Many biological drugs and sustained-release drugs cannot be satisfactorily delivered using current technologies. A number of devices and technologies in development are claiming viscous delivery, but none quite achieve the properties of the Oval device, particularly for sustained-release drugs.

Oval’s technology has enabled the delivery of previously undeliverable solutions, in a user-friendly device. The delivery of viscous drugs was successfully achieved due to a change in materials, a fundamental change in the plunger by using cup-seal and foil, and the ability to customise many aspects of the device including power source.

Usability is imperative in the design of auto-injectors and even more so where high viscosity drugs are involved as they create additional challenges. At Oval usability is integrated in the design from the outset. In addition to providing a solution to the delivery of viscous formulations, Oval has developed a technology platform that improves delivery performance and product reliability for the widest range of formulation viscosities.

Oval is able to test the rheological properties of drugs in-house, and using mathematical modelling can give clients a good indication of how their drug may perform using its technology.

REFERENCES