CAMBRIDGE DESIGN PARTNERSHIP

FORMULATION & DEVICE DEVELOPMENT: A SYMBIOTIC RELATIONSHIP

In this article, Caroline Zakrzewski, Drug Delivery Devices Scientist at Cambridge Design Partnership, considers the interaction between formulation and device development and the challenges that drive innovation in the field. Her work frequently sits in the overlap between formulation and device development, navigating the interwoven steps that lead to the sweet spot, where formulation and a device work in tandem, providing safe and effective delivery of the drug.

It's often been said that formulation development would be easier with the "final" device, and developing the device would be easier with the "final" formulation. It's a nice idea, but it could miss the symbiotic effect that each can have on the other – driving innovation in both fields (Figure 1).

Here we will explore some of the key topics that arise when developing a drug and device combination product, and how the iterative development of formulation and device can be beneficial for all the key stakeholders.

PRIMARY CONTAINER SELECTION

In its most basic presentation, a liquid formulation can be stored in a vial or ampoule and extracted by a syringe just before administration. This is easy to manufacture but does not consider all the needs of the end user. It was the method used 100 years ago, when the first insulin injections were carried out in humans and, whilst the fundamental mechanism remains the same, the development in primary containers has significantly improved.

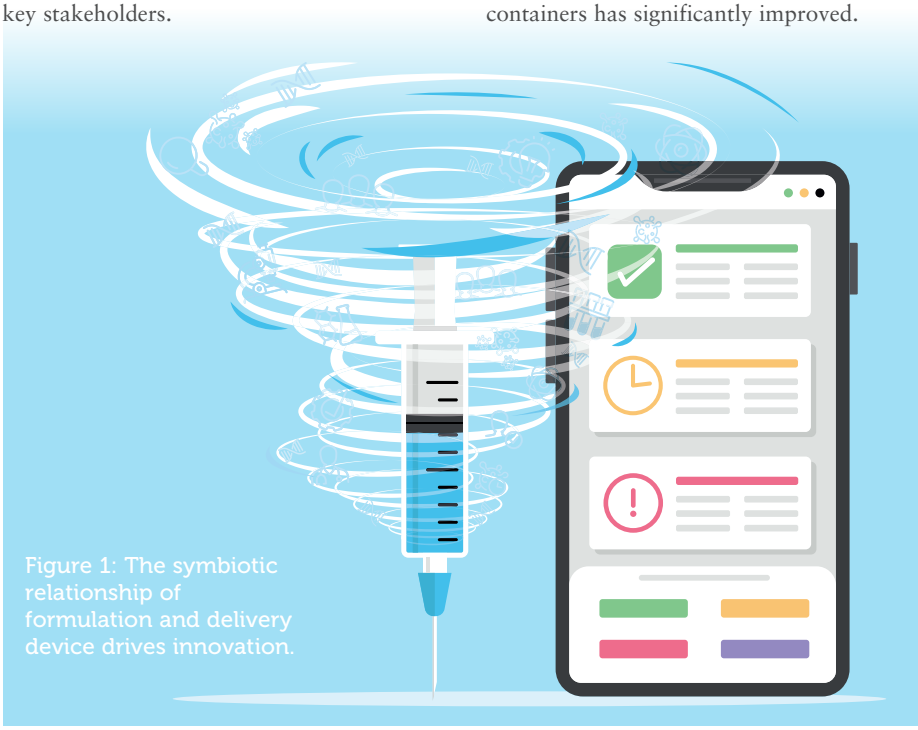

Figure 1: The symbiotic relationship of formulation and delivery device drives innovation.

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Most primary containers used for storage of small-volume injectables are made of glass. The formulation's influence on the choice of glass primary container can be as simple as UV sensitivity, driving the use of amber ampoules or vials, or more complex, with interactions on a molecular level seen with silicone or tungsten oxides. Commonly, liquid silicone is used to coat the inside of syringes and cartridges so that the plungers can advance to administer the dose. The silicone can form microdroplets in the formulation, providing nucleation sites and initiating agglomeration of larger molecules, such as biologics. Overcoming this interaction may involve moving to a primary container coated with baked-on silicone, which is chemically bonded to the glass surface, or to more recent silicone-free developments such as the GORE (Newark, DE, US) ImproJect Plungers with Schott's (Mainz, Germany) syriQ BioPure® silicone-free syringes. There's a similar consideration for the sensitivity of the drug to tungsten oxide residues deposited during the glass-forming process. Spiking the formulation with representative residues can give an early warning of whether this will be an issue, and alternative manufacturing methods can be used, although this increases cost.

The requirements for a sterile, single-use syringe to draw up from an ampoule or vial led to the development of plastic syringes, which are cheap to mass produce and customise, and much more robust for handling and transport. Typically made from polypropylene, these can be unsuitable for prefilled syringes (PFSs) because the moisture vapour transmission rate can cause concentration changes over time and absorption of the molecules onto the internal surfaces of the syringe can occur.

More recently, advances in polymer technology have sought to overcome these issues. Cyclic olefin copolymer (COC) and cyclo olefin polymer (COP) are gaining traction in the pharmaceutical industry as viable alternatives to glass PFSs. The tighter dimensional tolerances and more flexible customisations of these syringes give them advantages in more complex delivery devices, with a growing body of stability evidence behind them to address business risk concerns.

DELIVERABLE VOLUME

For subcutaneous or intramuscular injection, the delivered volume has perhaps the largest influence on the type of device selected to administer the formulation. There is a broad classification in the USP that small-volume parenterals are those which have a volume under 100 mL, but the volumes discussed here focus on the range of 0–10 mL.

Consider a delivery volume requirement of a straightforward liquid formulation. The most basic presentation would be a vial or ampoule and a syringe, where the vial (not reasonably constrained by size) could hold several doses. But what if this isn't suitable? As well as reducing the number of required components, PFSs reduce the number of use steps and the potential for use error associated with the vial and syringe presentation. However, they do bring additional challenges related to formulation stability. The requirement to be able to inspect the contents of the syringe prior to administration prevents the use of amber-coloured materials, which would have been present in the vial format to prevent the formulation being degraded by UV light. This can be resolved either through tertiary packaging or changes in the formulation – the former being easier than the latter.

PFSs can be used on their own or within autoinjectors that carry out many of the use steps required in a repeatable and reproducible way, improving patient compliance. It's possible, as shown by Teva (Petah Tikva, Israel) with Copaxone® (glatiramer acetate injection), to launch the PFS as a stand-alone presentation prior to investing in the development of an autoinjector. Most autoinjectors currently on the market are for delivery volumes up to 1 mL, either subcutaneously or intramuscularly. There are systems that can deliver larger volumes, but these come with challenges; a high flow rate during administration can cause local pain and discomfort at the injection site, and for slower flow rates it may be difficult to maintain the injector position for the time it takes to inject.

As the delivered volume requirement increases to 2 mL and above – particularly common in biologics – there's a decision to be made. With an injection of up to 2 mL completed within 15 seconds, the reaction of the injection site to the introduction of this volume becomes a factor in the ability to effectively deliver the formulation. The 5 mL subcutaneous injection of Roche's (Basel, Switzerland) Herceptin (trastuzumab) has shown that changes to the formulation, such as the addition of hyaluronidase, can help subcutaneous dispersal, but this isn't always possible or acceptable to the patient. There's a tendency to increase the formulation concentration to reduce the volume, which can be effective but goes hand in hand with an increase in viscosity. Increasing the viscosity affects the force required to deliver the formulation, particularly through thinner needles, hindering the appropriate administration in a manual injection and stretching the capabilities of many autoinjectors. In response to this, thin or ultra-thin walled needles have been developed, but there are physical limits constraining innovation in this area.

If the requirement is for delivery of more than 2 mL, particularly for a subcutaneous delivery, it's sensible to consider whether a bolus injector would be appropriate. Attached to the body for a short period of time, these devices deliver a larger-volume injection over a set time of minutes or hours, and have capacities up to 10 mL, sometimes more. Examples of these types of injector can be seen in the development of West Pharmaceutical Services' (Exton, PA, US) SmartDose®, the Enable Injections' (Cincinnati, OH, US) delivery device and BD's Libertas™. In a similar class are the ambulatory pumps which provide a consistent, fixed-rate infusion of a drug into the body and are commonly used for insulin delivery.

DRUG CHARACTERISTICS

So far, the consideration has been for formulations that are stable as liquids, but this isn't always possible due to either the nature of the active ingredients or the time available in development. The current crop of covid-19 vaccines is a good example of this latter point.

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Lyophilisation is a well-established process with the drug presented to the user in a dry powder form for the addition of a diluent to reconstitute the formulation immediately prior to administration. The knowledge and experience of manufacturers around the lyophilisation in vials, as well as the capital investment needed for the infrastructure to support this, creates inertia in the introduction of this type of formulation. The number of use steps required for reconstitution is significantly more than for just a vial drawn up into a syringe, requiring transfer of the diluent from a second container followed by agitation to ensure a homogenous solution. This increases in significance if the resulting solution is to be administered in several small doses. The need for a more user-friendly administration of this type of formulation drove the development of dual-chamber systems and the devices that contain them. Taking inspiration from the PFS model, dual-chamber systems were developed to reduce the use steps and materials required to reconstitute and administer this type of formulation.

Dual-chamber systems contain both the dry powder drug and diluent in separate chambers during storage to maintain the shelf life and stability of the drug product and facilitate the integral reconstitution though a simple use step prior to administration. Common systems include a glass syringe or cartridge with an external bypass – a channel that allows the diluent to transfer past the separating plunger and into the dry powder chamber. Adding only enough components needed to facilitate the administration, devices such as Vetter's (Ravensburg, Germany) Lyo-Ject® embody the core functionality of this type of system. Systems such the Credence MedSystems' (Menlo Park, CA, US) Companion® series build on this principle, linking novel internal bypass technology with the passive needle safety that is becoming a requirement in many healthcare settings.

Like the PFSs on which they are based, dual-chamber systems are expanding into autoinjectors, with products such as Pfizer's Genotropin® (somatropin) pen guiding the user through the reconstitution steps and enabling them to dial subsequent doses for delivery. The challenge of the current dual-chamber systems goes back to deliverable volume. In the current format, the need for both the diluent and dry powder chambers to have sufficient space to contain the deliverable volume makes the devices bulky, particularly as volumes increase.

HOW WILL THE DEVICE BE USED?

The move towards more patient-centric treatments, where the patient is not constrained by having their treatment delivered in a healthcare setting or even by a healthcare professional, is driving innovation in both formulations and devices. This can be seen most clearly in the range of treatment options that exist for Type I diabetic patients. Although the basic vial and syringe format is still common, disposable and reusable injector pens, such as Eli Lilly's KwikPen (insulin lispro injection) or Novo Nordisk's NovoPen respectively, are widely available with on-body pumps, such as Medtronic's MiniMed™ providing additional options. The device developers have challenged formulators to develop insulin formulations that are stable at body temperature, to support the use of ambulatory pumps. In return, the formulators have challenged device developers to accurately deliver single doses of increasingly concentrated solutions, with the move from a standard U-100 to U-500 and even U-1000 formulations.

No discussion of devices would be complete without mentioning connectivity. The recent trend towards connected devices allows feedback to the user – normally using an app – on how well they are adhering to their regime. This can also provide information to the monitoring physician on the suitability of the treatment format, with the potential to provide in-market trends that drive further formulation and device innovations.

THE FUTURE

So, what is next? Innovation in formulations and their devices is far from finished, as therapies become more complex and current markets experience a trend towards patient-centric self-administration. We've seen how previous limits of acceptable subcutaneous injection have been stretched by Roche's 5 mL Herceptin (trastuzumab) formulation, how devices have assisted in the delivery of highly viscous formulations previously unable to be administered by manual injection, and how the introduction of integrated reconstitution has allowed patients more freedom over their treatment profile.

On the horizon are integrated systems that overcome the challenges still present in reconstitution by the patient, devices that help to maintain a formulation suspension over time in a bolus injector, connected devices that provide tangible data on patient compliance, and more cost-effective primary container technology to support the next generation of formulations.

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The challenges that formulators and device developers set for each other are driving innovation in the field, and it is exciting to play a part in this process.

ABOUT THE COMPANY

Cambridge Design Partnership (CDP) is an end-to-end innovation partner focused on helping clients grow. Some of the world's largest companies trust CDP to design and develop their most important innovations. Located in Cambridge (UK) and Raleigh (NC, US), CDP specialises in the consumer, healthcare and industrial markets. Its multidisciplinary teams have expert knowledge to identify opportunities and overcome challenges throughout the product development and manufacturing process.

ABOUT THE AUTHOR

Caroline Zakrzewski is a Science Consultant with Cambridge Design Partnership. Holding masters degrees in Chemistry and Pharmaceutical Engineering, she specialises in drug delivery devices. Her career includes the co-ordination of multidisciplinary groups involved in the design, development, industrialisation and commercialisation of PFSs, autoinjectors, pen injectors and a range of inhalation devices. Ms Zakrzewski has a keen interest in the establishment of robust processes to facilitate the technical transfer of products into manufacturing.