RECONSTITUTION DEVICES: MIXING, POWER, PACKAGING & REGULATION

In this article, Charlotte Harvey, Consultant Mechanical Engineer, Sagentia, discusses the challenge of reconstituting lyophilised drugs, both from the perspective of the drug itself and the delivery device associated with it.

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Reconstitution devices are an ever-growing device category, due to the rise of biologics and the use of lyophilisation (freeze drying) to achieve their long term stability. With the number of lyophilised drugs on the rise, users (increasingly patients or carers in a non-clinical setting) are frequently faced with the burden of manual reconstitution. This raises usability issues around not only convenience, but also safety.

Thankfully, devices such as prefilled dual-chamber syringes are emerging to deal with this issue. However, these, and devices like them, have yet to become commonplace. An all-in-one reconstitution and injection device which removes responsibility from the user is the ideal. Here we will discuss the challenges of designing such a device.

This article will first address the challenges of reconstituting a previously lyophilised drug regardless of the delivery device in which it is to be used, before turning to the device itself – its design, primary packaging, power density and associated regulatory issues. What is not addressed here are the usability challenges that a standard injectable drug delivery device presents, such as pain management, preventing needlestick injury, the number of user steps and injection rates.

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THE CHALLENGES OF MIXING

Before we turn to the design of the reconstitution device itself, we must first consider the need to mix the drug safely and effectively. The basic steps of manual reconstitution are described in Box 1. However, each lyophilised drug has different properties which will affect how easily it dissolves. Where these properties have been deliberately controlled by the formulation chemist, they are likely to have been optimised for a particular mixing methodology. The properties requiring consideration are:

- Particle size (smaller particles will present a high surface area and therefore promote dissolution)
- Drug type (larger biomolecules tend to have a higher propensity to denature in certain environments)
- Physiochemistry (e.g. drug polarity; protonated versus free base)
- Formulation additives (additives to prevent caking or aid dissolution for instance)
- Diluent pH or ionic content
- Viscosity of the resultant solution.

These properties create the boundaries which the product design must work within. It is good practice to work closely with the formulation team in order to understand the properties of the drug fully and to build a device which accommodates these characteristics.

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Optimising Dissolution

Dissolution will occur even without any mixing. However, a boundary layer may form between the constituents, consisting of a saturated solution of the powder in the diluent. In order for dissolution to complete, the drug particles must diffuse through this boundary layer, making this a slow process. When we intervene by mixing a solution, we are attempting to break up this boundary layer and prevent the diffusion limit of the drug being the limiting factor in dissolution speed. This can be done either actively or passively.

Active mixers physically move the fluid, producing turbulence to promote mixing; a magnetic stirrer bar or an ultrasonic mixer would fall into this category. Passive mixers fold the solution together as it is passed through static channels. In the case of reconstitution, we typically avoid passive mixing methods, which require two fluids as the constituents.

In the process of mixing and breaking up the boundary layer, we are also physically moving the powder and diluent until they are adjacent, causing new boundary layers to form which are then, in turn, broken up. This physical moving of the drug constituents allows dissolution to occur quickly. To maximise efficiency, the mixing method should act upon the entire volume of the liquid. When a stirrer has not been designed properly, it only moves fluid in its immediate area, rather than promoting mixing throughout. This will most often occur when the solution has a high viscosity.

Introducing Turbulence to the Mixture

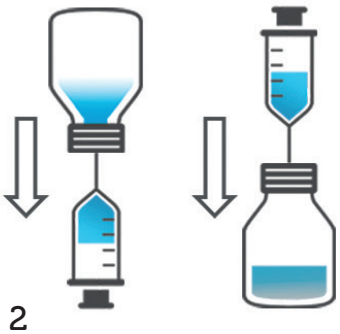
Effective mixing requires turbulent flow, making high viscosity one of the hardest drug characteristics to overcome. At a high enough viscosity, the device may be incapable of holding enough energy to take the fluid flow out of the laminar region. Even if you can provide enough energy to the solution, care must be taken that the energy input is not going to denature the drug by creating a high shear environment. For large biomolecules, this may become a significant concern, and thus mixing must be gentle. It is for this same reason that high temperatures must also be avoided.

Energetic mixing may not just risk denaturing the drug, it is also likely to cause foaming. Foaming is already a concern with manual reconstitution methods, hence users being instructed to swirl the mixture, rather than shaking it. It is also worth noting that

BOX 1: BASIC STEPS OF RECONSTITUTION

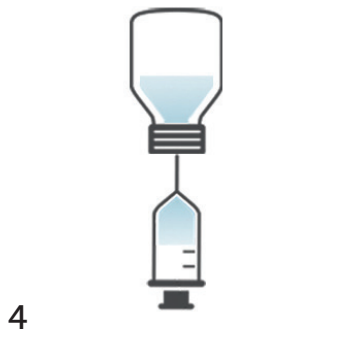
The user starts with a diluent vial, a drug and an empty injection syringe. In this instance, all diluent is to be mixed into a powder.

Diluent is moved from its vial into the powder vial via the syringe, typically using a large-gauge needle. The user should inject air into the diluent vial first to help with emptying. When emptying the vial, it should be held upside down, and moving air to the syringe should be avoided.



The vial containing both powder and diluent is swirled until the constituents are mixed. Gentle movement is used to avoid foaming. The user keeps doing this until no solid particles can be seen, possibly taking several minutes.

The reconstituted drug is withdrawn into the syringe for injection. The needle will need changing to a small gauge prior to injection.



it is much easier to mix a solution when air is present, the addition of air to the mixture further promoting turbulence. However, to avoid foaming and the formation of bubbles, we can attempt to remove the air from the mixing chamber. That may not be effective, however, as air may be released when diluent is introduced to the powder.

By minimising the volume of air, we leave ourselves with two potential mixing methods. The first is a stirrer of undetermined geometry which sits in the solution and manually moves the powder and diluent to mix. The second is ultrasonic mixing, which has the benefit of not touching the drug. As it creates turbulence through micro-cavitation, it might also blast apart any large chunks of lyophilised solid, further increasing the rate of dissolution by increasing the contact surface area.

The core mixing technology which the device is based on must work with the characteristics of the drug at hand. A balance must be struck between the speed of mixing, the energy available and the number of interactions required of the user.

CHOOSING A PRIMARY PACKAGING SOLUTION

When it comes to primary packaging, there is a choice to be made between standard vials, cartridges or syringes and something custom made. Custom solutions, either on the market already or currently in development, include bags (which are easier to fill without a large air volume) and moulded plastic containers (which allow the designer to integrate the drug container into the device's workflow better). In this section we will discuss how to make that choice.

Although custom primary packaging is becoming more prevalent, it is still far more common for commercial concerns to restrict design to the use of off-the-shelf packaging such as vials, cartridges and syringes. These concerns typically relate to the need for the requisite regulatory approval and the time and cost associated with acquiring it. Such expenditure would be particularly wasteful when designing a device for an existing drug.

The Problem with Standard Primary Packaging Solutions

Vials are the standard container for a lyophilised drug, and it is immediately evident that their size and shape is problematic. If we want our device to be capable of performing both reconstitution and injection, fully incorporating a vial will make our hand-held device too large. To get around this, the vial can be attached for reconstitution and then detached prior to injection. Alternatively, reconstitution and filling of the handheld device can be performed via a base station designed to have minimal drug contact. Either solution has the issue of adding further use steps.

Vials can also be problematic due to the large volume of air they contain. The drug will need to be drawn from the vial (probably into a syringe rather than directly into the body) whilst also avoiding removing a large portion of air. The level of concern we have here depends on the injection site (since the majority of user-performed injections are subcutaneous we will not spend much time on air injection in this discussion), but minimising air injection is always a priority. Use of a base station helps here as the orientation of the vial can be controlled, and therefore the volume of air that is removed.

Cartridges and syringes are smaller and more suitably shaped for a handheld device. It's also likely that they will be approved for use with an existing drug. However even these will hold a small amount of air under standard filling processes and this will need to be minimised if the user is going to inject from them directly – it will be difficult to control the orientation of the drug container in this instance. Additionally, accommodating our mixing methods inside these containers can be a challenge due to the shape and size available (long narrow cylinders allow for only a limited range of flow patterns). Note that a physical mixing element must be collapsible if held in the injection chamber and an ultrasonic transducer requires close coupling to the drug container to be effective. Neither solution works perfectly with these standard packaging options.

Custom Solutions

Custom primary packaging allows us to address many of the issues discussed so far. We can create a more desirable size and shape, allowing for efficient mixing within a handheld form factor, and we can minimise the presence of air inside our device, either through the filling process or by removing air after mixing. However, challenges begin to arise when we look to develop our filling process, as it is very hard to deviate from the established norm. Standard filling lines are

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a deeply ingrained part of an industry for which there are many barriers to change; in this instance because the change would require a significant investment of time and money.

We therefore have to make sure to include some geometrical constraints on the custom primary packaging. There are several questions that require answering if a custom primary packaging solution is to be manufactured successfully, for example:

- How close can the containers sit together?
- How large is the neck of the container?
- Will the custom packaging be able to withstand lyophilisation temperatures?
- Will elimination of the air in our container require an additional or new assembly step?

Any significant deviations from standard design are going to create requirements standard filling processes aren't used to; for instance, in a dual chamber syringe, a bung must be placed low down in the syringe barrel, whereas a standard filling process would require only a bung to seal the vial neck. It can therefore look tempting to lyophilise in a standard container and then move the powder to a new container. However, this is difficult when controlling for volume (and therefore dose).

User acceptance is likely to be lower when using standard primary packaging, so custom solutions should be sought. If commercial considerations make this impossible, consider moving away from a device which both reconstitutes and injects. Instead, have a base station which reconstitutes and fills a simplified injector. Due to the durability of the base station, we can add any additional functionality and complexity to that. If custom primary packaging is a viable option, we should aim to fit within the boundaries of standard filling processes as much as possible. If there is a need to step outside that, a filling contractor should be engaged early in the process.

POWER DENSITY

The main problem with the manual reconstitution process is the need for the user to go through a number of quite onerous steps. Therefore, so far, we have looked exclusively at fully-powered reconstitution and injection devices with the intention of improving usability.

However, given the number of steps involved in manual reconstitution, it would only require automating a few of these steps to see a significant usability improvement. We could therefore keep the mixing step as a manual process in order to reduce the power requirement of the device, thus reducing the device's power density. Given that, regardless of automation, it is a requirement for the user to be able to check that mixing has occurred effectively. It is not too burdensome for them to be fully involved in that part of the process.

If we do want to remove burden from the user via an automatic mixing procedure, it will be necessary to consider the size of the delivery device due to the power required. As mentioned previously, the properties of the drug itself will define the energy input required for effective mixing, but it could be a substantial amount. The introduction of batteries will also raise additional challenges, such as how they should be charged and disposed of. Large power requirements would most likely mean a larger device, which could become difficult to hold in the hand (once again the use of a base station can solve this problem, but this is not always a viable solution). Battery sizes can be minimised by performing non-mixing functions without electrical power, using springs for actual drug delivery for example.

REGULATORY REQUIREMENTS

Finally, there are regulatory requirements to consider, which will have a bearing on the method chosen for overcoming the technical challenges discussed prior. For instance, the user has to be able to see the quality of the mix, meaning that there must be an optical path through to the drug. Then there are requirements around patient safety, ensuring delivery of the full dose, proving that the mixing method is effective and validating any new materials put into contact with the drug. These requirements around the mixing mechanism may not be familiar to those designing more conventional drug delivery devices and will require necessary analytical testing and human factors studies before incorporation into the device development plan.

ALL-IN-ONE RECONSTITUTION & INJECTION

The reconstitution of lyophilised drugs by a non-medical professional raises a series of challenges around effective mixing and safe administration, whilst also minimising the burden on the user. The product development process must weigh up these various factors and assess the degree of development and manufacturing effort needed to produce something novel. An all-in-one reconstitution and injection device will produce the biggest improvement in patient outcomes for those using them. For this reason, it is an area of the drug industry where we are likely to see significant innovation in the coming years.

ABOUT THE COMPANY

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Sagentia employs over 150 scientists, engineers and market experts and is a Science Group company. Science Group provides independent advisory and leading-edge product development services focused on science and technology initiatives. It has 16 European and North American offices, two UK-based dedicated R&D innovation centres and more than 400 employees. Other Science Group companies include OTM Consulting, Oakland Innovation, Leatherhead Food Research and TSG Consulting.

ABOUT THE AUTHOR

Charlotte Harvey is a consultant mechanical engineer at Sagentia Ltd. Her experience lies predominantly in managing medical product developments, specifically those in the surgical and injectable drug delivery fields. Recent projects have included front-end innovation in the drug delivery space, user interviewing for human factors, and several instances of developing reconstitution-based autoinjectors. Charlotte graduated from the University of Cambridge (UK) with a Masters in Mechanical Engineering.