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Whitepaper

Achieving faster formulation of solid oral dosage forms for First-In-Human supplies using drug-in-capsule approach

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Introduction

The pharmaceutical industry is increasingly looking for approaches to shorten drug development timelines and save on cost, especially virtual biotech companies who rely heavily on key milestone payments. It is therefore imperative that new chemical entities can be quickly manufactured quickly into clinical drug products.

Across the industry there are two principle approaches to formulation development of solid oral dosage forms for First-In-Human (FIH) studies, namely the "commercial formulation approach" and the "exploratory formulation approach".

This article is broadly broken-down into two areas; the direct and indirect cost savings associated with the "exploratory formulation approach" and how systems such as the Xcelodose® 600S mitigate against some of the risks associated with using the "commercial formulation approach" in early development.

Overview of existing industry approaches:

The commercial formulation approach advocates a clinical formulation that will bear resemblance to commercially acceptable formulations, which for a solid oral dose will most commonly take the form of a capsule or coated tablet. The goal in developing this first generation formulation will focus on ensuring that it is "fit for purpose" for Phase I and II clinical studies. When performed well there is a strong possibility that the development work will provide a strong starting point for development of a formulation for late stage clinical development and registration. The challenge here is to select a dosage form that can reach later-stage development, quickly, and in a cost effective manner.

The exploratory formulation approach favours the use of the simplest possible formulation such as powder-in-capsule. In its simplest form this will be API-in-capsule. Use of API-in-capsule has seen a significant growth in popularity over the last 5-10 years, not least because of the arrival of systems which enable automated and accurate filling of relatively large quantities of API-in-capsules, such as the Xcelodose (Capsugel, Cambridge, United Kingdom) or Fill2Weight® (3P Innovation Ltd, Warwickshire, United Kingdom).

Directly filling API into a capsule is probably the quickest option for entering clinical trials, as this method requires little or no excipients – potentially saving 3-4-months of formulation development and stability testing.

Contrary to what many people believe, pursuing the "commercial formulation approach" for FIH studies will not necessarily place supply of drug product on the critical path of the overall development timeline. Assuming good planning by the Project Manager, a formulation can be developed and stability data generated in parallel to preclinical toxicology studies, which in general takes 4-6 months to complete.

In the context of overall development costs, direct outlays associated with pursuing the commercial formulation approach are generally not significant relative to the overall cost of a development programme. Also, investment in a robust formulation can increase the attractiveness of the overall package if out-licensing is planned after early development. A well-developed commercial type formulation can also offer future benefits in terms of time and cost when larger volumes of clinical supplies are required. None the less, in an environment where development budgets are tight and where there is pressure to minimise development spend before proof of concept, the direct and indirect cost savings associated with adopting an API-in-capsule are attractive to many.





But is API-in-capsule always a suitable approach?

At Almac, the decision on whether API-in-capsule is a suitable approach, is made during up-front assessments by a multidisciplinary project team - including CMC experts from Chemical Development, Solid-State Chemistry, Formulation Development, Analytical Development and Project Management. Firstly, the multidisciplinary team scrutinizes the data to ensure that the API is suitable for an API-in-capsule presentation.

If the API possesses poor physicochemical properties (e.g. poor aqueous solubility such as Biopharmaceutics Classification System class II or IV compounds), then API-in-capsule may not be appropriate, as some formulation development work will be required to investigate the potential benefits of functional excipients, such as solubilising agents, which may be required to improve bioavailability. This is an important point, as too often organisations in a hurry can overlook the potential impact of the API properties when determining their pharmaceutical development strategy and API batch sizes. Whilst all the information may not be available, sufficient data will have usually been generated during the lead optimisation stage of discovery to enable an informed prediction on the likely formulation strategy.

Another property to consider is the bulk density of the API as most API-in-capsule machines do not possess a 'tamping' feature. Consequently, the bulk density and the way the drug particles pack, have a direct effect on the amount of API that can fit into a capsule. Therefore, the dose is essentially limited by the size of the capsule.

It is well known that micronised powders possess poor flow properties and this can result in issues with both the API-in-capsule machines and capsule boards. For example, the high throughput unit (HTU) of the Xcelodose® automatically refills the dispense head with API but a certain degree of flowability is required so that the API can be transferred from the HTU hopper into the dispense head.

Capsule boards can also be affected by poor flow properties as the filling process can be irregular leading to variability in dose/fill weight. Not only is the particle size of the API to be considered when determining if API-in-capsule is a suitable strategy, but the distribution can also have an influence.

If the API possesses a wide particle size distribution, then it may not be suitable for the Xcelodose®. Potentially small particles may pass through the dispense head into the capsule with the larger particles retained. This can lead to frequent interruptions to stop and clean the dispense resulting in increased downtime. It is worth noting however, that careful selection of the dispense head and sieving the API to narrow the particle size distribution can assist in overcoming this issue.

In summary, if the physicochemical properties of the API are good, then API-in-capsule using manual fill, capsule boards or Xcelodose® system should be possible. Consideration should also be given to the likely doses and the quantity of capsules required in determining whether the Xcelodose® is an appropriate piece of equipment to use.



Xcelodose 600s

Direct cost savings with API-in-capsule using the Xcelodose®

API usage

In early development, API is usually in short supply with material being needed for toxicology and DMPK studies, analytical development, API characterisation studies and formulation development. Although API is usually relatively expensive at this stage of development, one of the benefits of the Xcelodose system is that only small quantities of API are required to determine operating parameters.

Typically ~5g of API is required to develop Xcelodose filling parameters, such as, tap frequency, pulse width, amount of slow tapping and high throughput unit settings.

Compared to usage expected by developing a dosage form using the “commercial formulation approach”, 5g is accepted as a reasonable amount of API for drug product development. Furthermore, from a scheduling perspective, development of Xcelodose® operating parameters can be left until immediately prior to GMP operations - meaning that the Project Manager has one less aspect to worry about when allocating API from earlier development batches.

Direct labour hours

Four to six weeks of development time is usually required for a “fit for purpose” formulation in early development following the commercial approach. Although the formulation scientist will not be ‘hands on’ throughout, they will be reasonably busy interpreting excipient compatibility data, manufacturing prototype blends and stability batches of the dosage units and writing protocols/reports. In contrast, API-in-capsule negates the initial need for lengthy excipient compatibility, blend feasibility and probe stability studies.

In order to manufacture API-in-capsule supplies for clinical use, traditional methods have included hand-filling, and occasionally, the use of capsule boards.

Hand-filling is certainly not rapid, if the weight required is low (for example, tens of milligrams or less) this filling process may take up to five minutes per capsule. Capsule boards can produce filled capsules quicker than hand-filling, but can result in a significant loss of API as the process is not particularly “clean”.

A further problem is that the use of capsule boards does not lend itself to low dose fills, as small volume dosing plates can lead to non-reproducible fills particularly for poor flowing APIs. In contrast, the Xcelodose can fill a wide range of weights, including very low weights both accurately and relatively quickly. Once a suitable set of parameters has been developed for the API in question, there is little need for direct labour.

Indirect cost savings

In addition to the direct cost savings outlined above, there are many more indirect savings that can be achieved by using an API-in-capsule approach. Some of these are highlighted below:

Analytics

Simplifies analytical development

The analytical methods that have been developed for the API will most likely be suitable, with little or no analytical development. In the majority of cases, one would not expect specificity issues, making the assay method particularly straightforward for the analytical group. If the API is particularly soluble in acid conditions one could argue that the API-in-capsule approach can remove the need for a dissolution method.

Immediate stability data access

Typically for API-in-capsule drug products, our clients focus their Clinical Trial Application (CTA) stability justifications around the drug substance stability data. This data is used as primary evidence to justify shelf life for the drug product. Typically, when this strategy is employed, clients commit to a CTA that places the API-in-capsule clinical batch(es) on storage, providing updates to the CTA as data becomes available. This strategy helps accelerate the programme through to clinical trial, as there is no need to wait for product stability data to become available.

Cleaning methods

The cost of replacing the contact parts on the Xcelodose is significantly cheaper than the cost required to develop a cleaning verification method.

Another consideration is time; developing a cleaning verification method can take weeks of work, which is time that could be spent developing the Xcelodose method and indeed, starting manufacture of the clinical product.

Ease of containment

A lack of toxicity data for compounds entering FIH studies is common and therefore to ensure operator safety protection, the Xcelodose can be used within the Xcelohood®. This means potentially toxic compounds can be easily contained within the system.

Mitigation of risks associated with the “commercial formulation approach”

It is not uncommon in early development to encounter differences in particle size, hygroscopicity, polymorph content and crystallinity of the API. Such changes in the API during chemical development can result in ‘headaches’ for the multidisciplinary team working on the ‘commercial formulation’ approach. For example, a change in flow properties can affect blending time, roller compaction settings and compression of encapsulation parameters, resulting in lengthening timelines, more development work and therefore increased costs.

Physicochemical characterisation is still extremely important and API properties can have a significant effect on the processing parameters for the Xcelodose. However, a change in API characteristics when using this approach would most likely result in only 1 or 2 days of additional time for optimisation of Xcelodose processing parameters.

Blending excipients and a drug together can be difficult, especially when attempting to attain uniformity at low starting doses. Segregation of the components, sampling bias and the need for a blend uniformity method, are all challenges associated with the commercial approach. All of these factors are negated with the “exploratory formulation approach”.

Case study 1

A client approached Almac to request supplies for a FIH study. Initial requirements were for less than 1000 capsules of two different dosage strengths. No formulation studies were to take place, as the client wanted to save time and API for reasons outlined previously. A decision was taken to manufacture these supplies manually using an analytical balance. The client subsequently requested a re-supply of 25mg and 100mg capsules in quantities of greater than 10,000 and 5,500, respectively. It was quickly decided that an automated process was the best solution for manufacture of re-supplies.

The API possessed poor flow properties and was treated as a potent compound (Operator Exposure Limit of between 0.1 – 10 ug/m3) due mainly to the lack of toxicological information available. This re-supply project was therefore a good fit for the Xcelodose® system, in combination with the potent handling capabilities of the Xcelohood®.

From the solid-state characterisation package, the particle size distribution of the batch of API to be used for the re-supply is shown in Table 1:

Table 1: Particle size distribution data	
D10 (µm)	1.45
D50 (µm)	9.85
D90 (µm)	23.88

This information, coupled with flowability data, suggested that the API possessed poor flow properties. Although poor flow does not impact hand-filling, it was thought that poor flow may cause issues with the Xcelodose®, particularly when using the high throughput unit, where the API must flow from the hopper into the dispense head. However, with this API, it was possible to adjust the frequency of the vibrations and the angle of the hopper to allow a reasonable flow of API into the dispense head.

Using the Xcelodose® 600S the required quantity of capsules were completed within three weeks (single shift, 40 hour working week). Less than one day was required to determine suitable processing parameters for the 25mg and 100mg strengths.

If manual capsule filling had been used for this resupply it would have required approximately 500 hours in total to produce the required number of capsules fill (see Figure 2).

It is also worth noting that as commonly seen with FIH studies, there was a lack of toxicology information about the API. Therefore, in order to ensure protection of our operators, the original supplies were manufactured within a ventilated balance safety enclosure (VBSE). However, because the analytical balance was in direct contact with the VBSE, any vibration from the unit resulted in difficulties with balance taring. For the re-supply operation, the Xcelodose® was used within the specially designed Xcelohood® system. As the Xcelodose® is not directly in contact with the Xcelohood®; the micro balance used by the Xcelodose® is inherently more stable and results in much quicker taring.

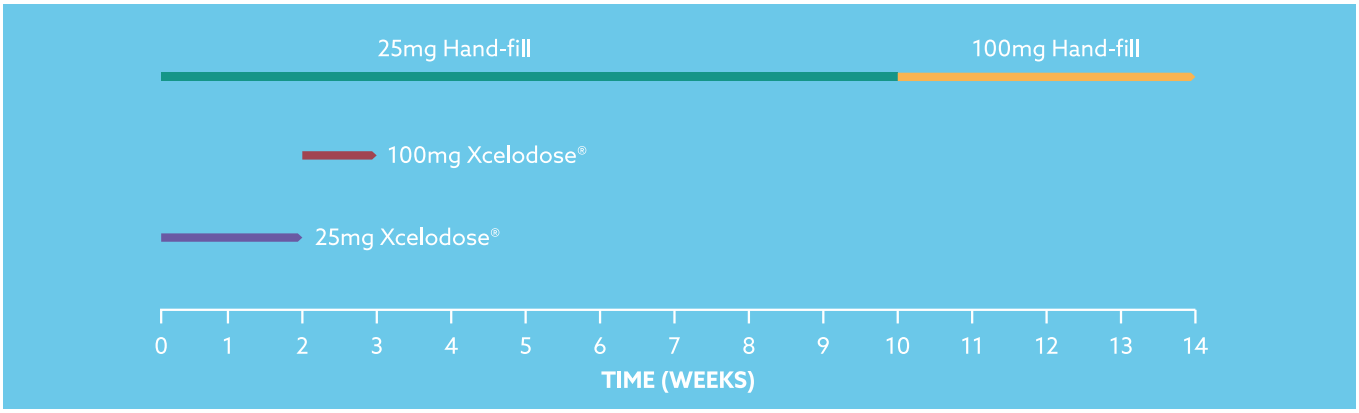


Figure 2: Timelines using the Xcelodose® compared to hand-filling

Case study 2

Delayed introduction of “commercial formulation approach” and use of drug-in-capsule to supply larger clinical trials.

Almac has a number of clients who are delaying the introduction of the ‘commercial formulation approach’ and instead use the Xcelodose® to manufacture larger volumes of clinical trial materials. This can often be a deliberate decision to delay development of a commercial formulation approach until later clinical milestones have been achieved in order to realise the direct and indirect costs savings covered earlier in this article. On some occasions the requirement for larger volumes of ongoing supplies are borne out of necessity to support post trial access of a drug which has proven successful in initial clinical trials (E.g. extended access programmes).

One client approached Almac to request the Xcelodose manufacture of a substantial re-supply of capsules for an ongoing clinical trial (80,000 capsules of a low dose and 60,000 capsules of a high dose).

This was scheduled into two campaigns over a six month period in order to maximise shelf-life but still meet clinical demand.

One point for consideration was the fact that multiple batches of API with slightly different physical characteristics were supplied throughout the campaign and therefore Xcelodose® methods would have to be verified for each drug substance lot due to the potential for changes to impact the filling process. It is also worth noting that the Xcelodose® was not originally designed for such large batch sizes (30,000 capsules in some cases) nor for long periods of continuous operation (24 hours, 5 days per week for a number of months). At Almac we have addressed this by heavily investing in the training of our operations personnel to ensure they are capable of diagnosing and resolving technical machine issues in an efficient manner.

Conclusion

We have a number of approaches for the manufacture of supplies in FIH studies. With the increasingly favoured “exploratory formulation approach”, possible manufacturing options include hand-filling, capsule boards and systems such as the Xcelodose®. This article has explored the direct and indirect benefits of using systems such as the Xcelodose®. In the case study, the direct cost savings of the Xcelodose® were shown in terms of direct labour costs with clinical supplies delivered approximately 7 weeks earlier, than if a hand-filling operation had been employed. In addition, timelines for this project were aided further by the fact that no cleaning method was required, meaning development of the Xcelodose® process parameters could start immediately.

Finally, only 5g of API was required for development activities and coupled with minimal losses during processing, resulted in less API usage when compared to a hand-filling approach, and significantly less API usage, than would have been required for development using a “commercial formulation approach”.

To summarise, if the “exploratory formulation approach” is suitable in terms of API properties, then we have found the Xcelodose® system a viable option for the manufacture of supplies for FIH studies with opportunities to realise cost savings for our clients. However, if there is time, budget and API available, then we will work with client partners on a strategic “commercial formulation approach” to develop a suitable dosage form, fit for purpose and likely to support longer term clinical supply.



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Colin has a degree in Pharmacy from the Queen's University of Belfast and went on to complete a Ph.D. in Pharmaceutics. He has worked in the Pharmaceutical industry for over 20 years and has practical experience of interpreting solid state information pertinent to formulation development. Specialising in solid oral dosage forms, Colin has worked on many formulations for early stage development using various technologies. He also has previous experience of topical and controlled release formulations.

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