Beyond Fast Filling

The strategy of powder-in-capsule has the ability to accelerate the clinical development cycle. David Edwards of Capsugel investigates new developments on the drug market

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The early stage is a critical time during the development life cycle of a new drug. Like a newly hatched tadpole, it has to compete for resources, not only with its tadpole siblings, but with all the others sharing the pond in order to survive. No matter how large it is, the parent drug company has to choose which of its newly hatched drug candidates are best suited to survive and grow in the marketplace, and then direct available resources accordingly.

TIME IS MONEY

There are many resource constraints in early stage drug development, such as available drug quantities, testing personnel, equipment, funding and, perhaps most crucially, time. With a patent life of 20 years and a development timescale of 10-12 years, the window of opportunity for a drug is limited and it is imperative that the drug has enough time on the market to recoup investment and to be profitable in line with the company's needs. Any legitimate reduction in the development process can result in an extension of the profit window for the drug. Consequently, such shortcuts are avidly sought by R&D departments.

With this in mind, let's focus on one of the first key 'go/no-go' decision points for the new molecular entity (NME) drug candidate for many pharma companies – Phase I clinical trials, or 'First in Human' studies. Phase I includes the initial introduction of an investigational new drug into humans. These studies are closely monitored and usually conducted in healthy volunteer subjects, with a focus on safety. They are also often designed to better clarify the pharmacokinetic and metabolic properties of the drug. During Phase I, sufficient information should be obtained to permit the design of well-controlled, scientifically valid, Phase II studies.

The first-in-human hurdle is important for a number of reasons; it gives a first indication of tolerance and prospective efficacy in humans and, because trial participant numbers are typically small, the cost is relatively low. This means that a number of candidate compounds can be assessed for comparative viability without committing excessive financial resources. The faster this can be done, the faster less viable candidates can be eliminated, so the concept of 'faster-time-to-first-in-human' can also be construed as the rather negative sounding 'faster-time-to-fail'. Knowing that a compound will not make it any further to market will release precious time and other resources in order to concentrate on other NMEs that have potential, and will also reduce the risk of failure at much later and far more expensive stages of the clinical development process.

HISTORICAL CHALLENGES OF MICRO-FILLING

Much work has been done by pharma companies to speed up or improve R&D processes in order to reduce timescales, and real savings can be achieved with the use of new technologies. One, which has come to the fore over the last few years, involves dosing pure drug or active pharmaceutical ingredient (API) rather than formulated or blended product for production of Phase I clinical trial materials (CTM).

In the past, this strategy was employed rarely, primarily because of the difficult controls required to manually dispense many individual low dose weights. This had a

Figure 1: Building and breaking of micro-bridges

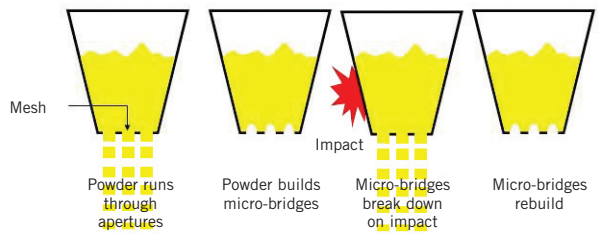
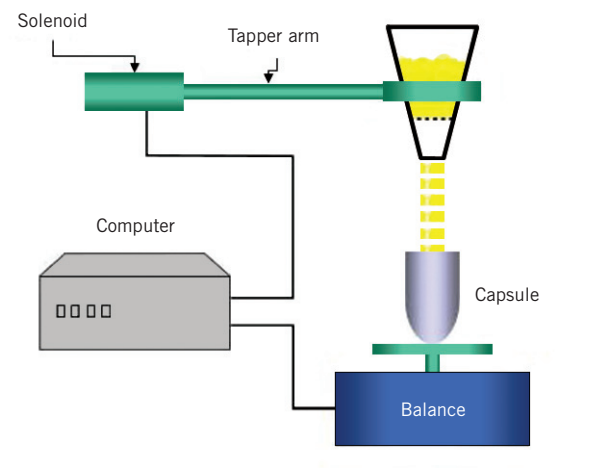
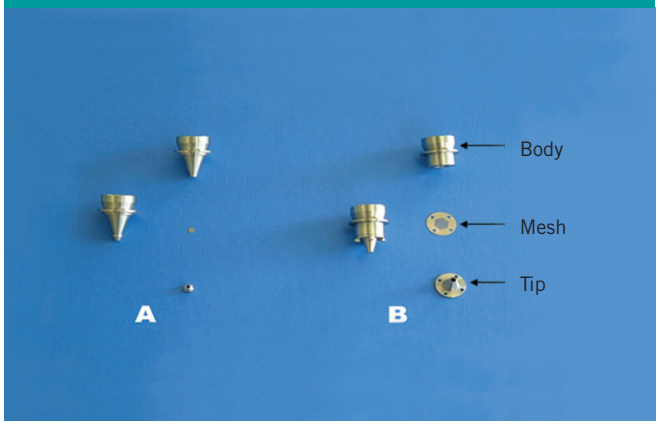


Figure 2: Weight control system



number of limitations, not least the sheer repetitiveness and ensuing error potential of a manual process which is extremely labour intensive. Weights below 10-20mg could not be reliably filled by hand with any accuracy or precision, and the losses were likely to be high. Often, with limitations on the amount of drug available, drug developers would blend or formulate drug product so that overall drug weights were easier to manipulate. The downside of this was that the resulting formulated product would require stability and homogeneity testing over a period of three to six months, thereby adding more time to the process.

Figure 3: Dispense head components



Another complication involves the container for the drug; the method of drug-in-bottle (aka powder in bottle) was, and still is, commonly used. This involves dispensing the drug, again by hand, into a suitable bottle, dissolving or suspending it in a vehicle such as water or methylcellulose, and administering it to the trial participant. This too has inherent problems, in addition to weight control, the ability to re-suspend and elute the entire drug is not easy and therefore can often be unpalatable.

LINKING SCIENCE TO SIMPLE PRINCIPLE

The advent of new dosing technologies, such as the Xcelodose system, has revolutionised this process. The technology involves the precise dosing of drug powder into capsules and other small dose containers by gravimetric means.

The technology makes the powder behave like a liquid, flowing through a mesh within a hopper or dispense head that promotes powder 'micro-bridges.' These micro-bridges break and reform if a shock or tapping action is applied to the outside of the hopper (see Figure 1).

On breaking the micro-bridge, a small amount of drug powder passes through the mesh and into a container. The action is similar to that employed in a pepper pot or pepper shaker. The amount that passes is remarkably consistent and is a function of the number of holes in the mesh, the diameter of the holes and the powder characteristics. The weight dispensed is controlled by a seven-place micro-balance, linked to a computer, which controls the amount of tapping when facilitated by a solenoid (see Figure 2).

The weight of each capsule is tared to zero, enabling the system to weigh and record API weight, with doses as low as 100mcg easily achievable for many powders. The machine uses a supervisory PC control algorithm to continuously monitor the weight being dispensed in real-time by adjusting the parameters that influence the flow rate. The amount of powder falling as a result of each tap being measured approximately 15-20 times per second. This enables the system to 'learn' how the powder behaves. By setting the machine to a target weight, together with pass/fail limits, the number of taps is controlled as the system adjusts accordingly. This will take into account whether the powder is free flowing, of even particle size, or if it comes out in lumps of uneven particle size. The tapping rhythm is initially applied at a fast rate to reach approximately 80 per cent of the target weight, and then switches to a slower rate to achieve precision of fill. Using this methodology, the system can easily achieve relative standard deviations (RSDs) of product weights below two per cent for most powders.

WORKING WITH MATERIALS OF VARYING PROPERTIES

Dispensing powders with different characteristics (for example, fluffy, cohesive, free flowing, micronised, and so on) is accomplished using a number of techniques, and industry feedback seems to indicate that, to date, provided a powder can be made to form micro-bridges, it can be dispensed using this technology, irrespective of particle size. This is accomplished by the availability of a wide range of dispense heads – see Figure 3.

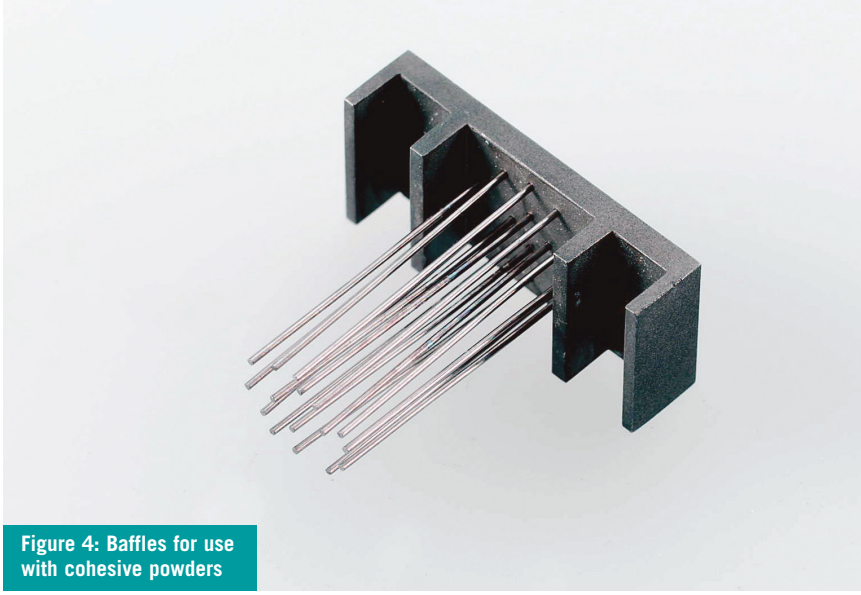


Figure 4: Baffles for use with cohesive powders

These heads differ with variants featuring small numbers of large holes or large numbers of small holes, varying body shapes and tips to best accommodate dispensing of the powder and the specific weight required. Dispenser heads with larger holes are usually used to dispense larger weights, with the converse also applying. Ideally, the dispensing time should be in the order of 5-10 seconds.

The technology can also be 'tailored' to the powder in order to give higher throughput or greater precision. Here again, additional techniques can be employed: speeding up or slowing down the rate of tapping; increasing/decreasing the force of the tap; and applying the use of baffles or stainless steel rods inserted into the powder within the dispense head to break up cohesive or sticky powders (see Figure 4, page 38). Beads and granules can also be filled using the system.

Using these techniques, the system can accurately and precisely fill weights within the range of 100mcg to several hundred milligrams. It does not employ a tamping mechanism, and consequently the actual amount of powder that will fit into a capsule is limited by the powder's physical characteristics. As the powder is tapped into the capsule, larger particle sizes fall and will be surrounded by considerable air space. In some cases, the drug substance may require pre-processing to increase density and enable high dose powder-in-capsule (PIC) formulations. Roller compaction followed by milling has been used in such applications (1).

FASTER FILLING: USING LESS API IN EARLY DEVELOPMENT

With its ability to dispense such small weights with accuracy and precision, the technology supports a material-sparing formulation approach, which enables scientists to decrease the time required for dosage form development by placing the drug substance into a capsule. Powder-in-capsule (PIC) reduces development time, conserves drug substance and allows better management of resources against compound attrition (2).

Blended or formulated product has also been successfully dispensed using this kind of technology. There are some limitations, but trials have shown that if the powder constituents are of approximately equal size, then the potential for segregation is minimised (3).

One model that has been developed is fully automated and is dedicated to filling capsules, both gelatin and HMPC, in a wide range of sizes (00-4). The use of capsules in Phase I studies is very commonplace, as these offer a convenient dose form which is both easy for the formulator to manipulate, and easy to swallow for the trial participant.

The system is completely automated in taking empty capsules, rectifying them into the correct orientation, separating the top from the bottom by the application of a vacuum, and filling into the base of the capsule, which has

been tared to zero on the balance pan. The filled capsule is then moved around on a carousel, re-united with its top, checked for length and sorted into accept ('good' receptacle) or fail ('bad' receptacle). The capsule can be deemed as a failure for a number of reasons, including: weights fall outside the limits set by the operator; capsule does not close properly; or the capsule is or is not present in its entirety.

This higher throughput system is largely dedicated to the manufacture of CTM samples, but has also been used for formulation development. Capsules are readily available in various sizes to accommodate differing doses and also are more patient-friendly by being easy to swallow and mask the taste of the active. Opaque capsules can be used to blind the formulation if desired.

By comparison, the second model features the same filling technology but is semi-automated – that is, the user loads the containers into the machine manually and removes them at the end of the fill. The advantage of this machine is its flexibility; it can be adapted to fill other containers as well as capsules. To date, the system has been used for filling cassettes for needle-free injection units and blisters for inhalation products. Other applications include vials and tubes.

Documentation and traceability of data is crucial for all CTM batches. This technology weighs and records the data for each capsule, including amount and time of fill, associated batch and run records, and any operator intervention during the run. The system records data for both 'within specification' capsules and 'outside of specification' capsules. The two groups are dispensed into separate containment units in the machine during use. The run records are produced in PDF format using a software system which is 21 CFR part 11 compliant, and which will allocate an electronic signature that is individual to each machine. Data is input via a human-machine interface (HMI), which is also used to control the functions of the machine. This unit is separated from the main dispensing unit by three meters of umbilical cable, which also allows the dispensing unit to be housed in a containment system, isolator or different class of air handling if so desired.

CONCLUSION

The novel concept of dosing pure APIs, making PIC dosing a viable strategy for clinical trials, offers real-time savings in the development process, particularly for Phase I trials. The technology is becoming widespread in its use throughout the industry, with many companies of all sizes (from small biotech to large pharma) using the technology for early stage studies. With the aforementioned extended downstream benefits, the concept of micro-filling can be expected to continue to grow, as it helps enable pharma R&D departments to remove the 'losers' and pick the 'winners' at an earlier stage, thereby giving the fittest tadpoles the chance to turn into fully grown frogs! ◆

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