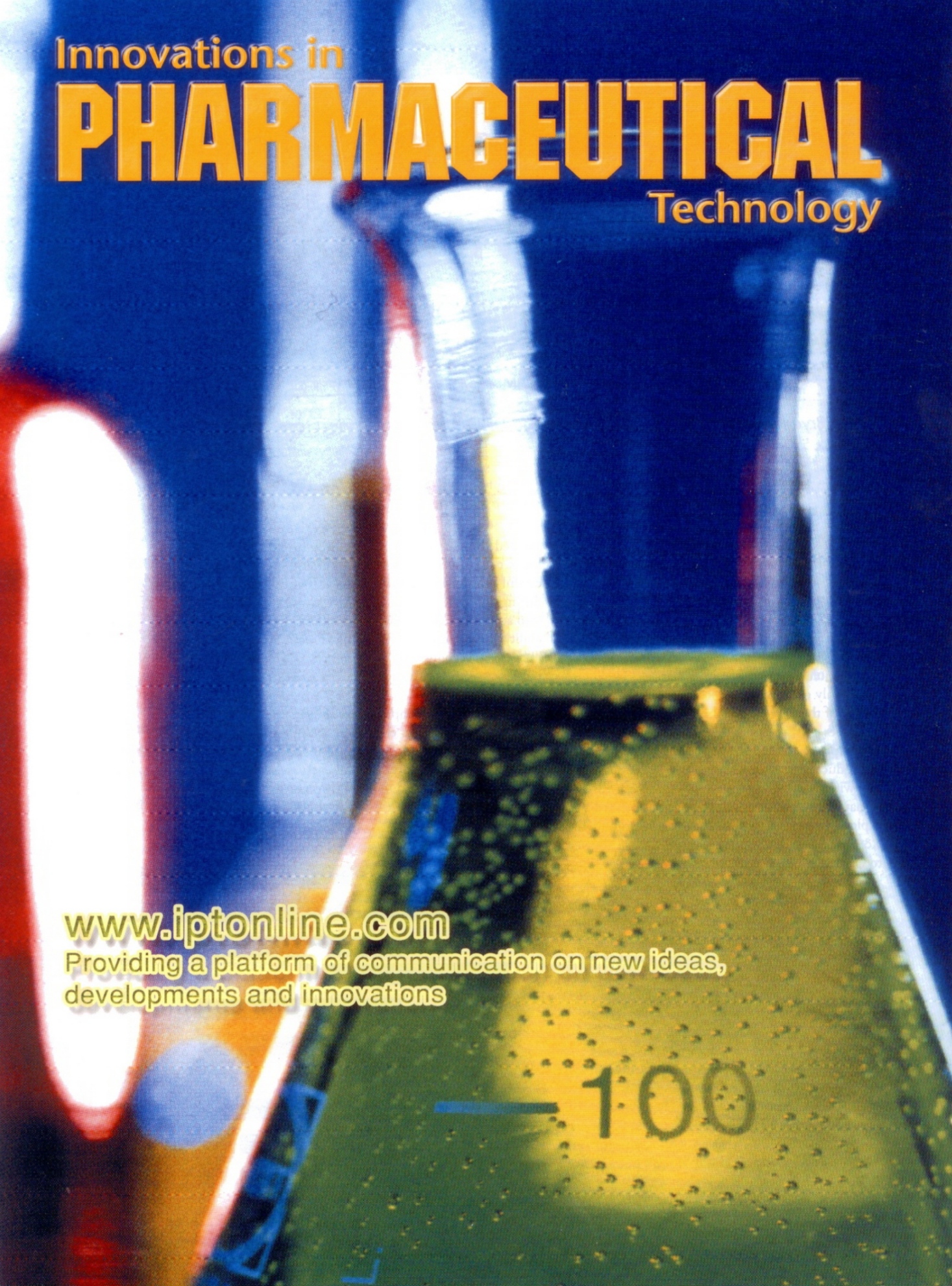
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Advances in powder-dosing technology

A new technology offers a "step-change" in the way that early clinical trial supplies can be formulated – resulting in real savings in development times and costs.

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Pharmaceutical companies are battling against time from the moment a new chemical entity is patented; the patent can protect their molecule from outside competition for around 20 years. This may seem like a long time but it can take 10 to 12 years to steer a compound from research through development and the regulatory process, into manufacture and finally to market. The figure commonly quoted as a typical cost for this process is now of the order of $500 million. This expenditure does not, of course, guarantee success in the marketplace, and history is littered with examples of products that have reached the market but failed following launch. Even if a product is successful, it may only leave a period of maybe 6 to 8 years to exploit the product commercially and recoup the R&D outlay before generic equivalents are allowed to enter the market and the price collapses.

As a result of this, most large pharmaceutical companies are taking a hard look at candidate compounds coming through their research pipeline. Most companies will not commit to R&D expenditure unless projected global revenues for a product exceed $500 million. The R&D Director for a pharmaceutical company is under pressure as never before in terms of identifying a potential blockbuster drug – one that has potential sales in excess of $1,000 million per annum. Not only are there intense commercial pressures, but other interested parties are all making greater demands in terms of safety and side effect profiles. These include the regulatory authorities, clinicians and even patients.

It is vital, therefore, that an R&D Director can not only identify a lead candidate for a blockbuster product – and sooner rather than later – but also to be able to 'kill off' compounds that will not succeed (for various reasons), in order to be able to focus time and resources on potentially more successful candidates. It is well known that time saved during the development process translates directly into additional sales through extended market availability and opportunity following launch. A typical increase in revenue may be as much as $1 million per day for a major drug product towards the end of its patent life.

Pharmaceutical companies are therefore having a tough time. They are constantly looking for ways in which they can cut down on the time required for development through to manufacture, as this is typically the longest and most costly phase for a drug

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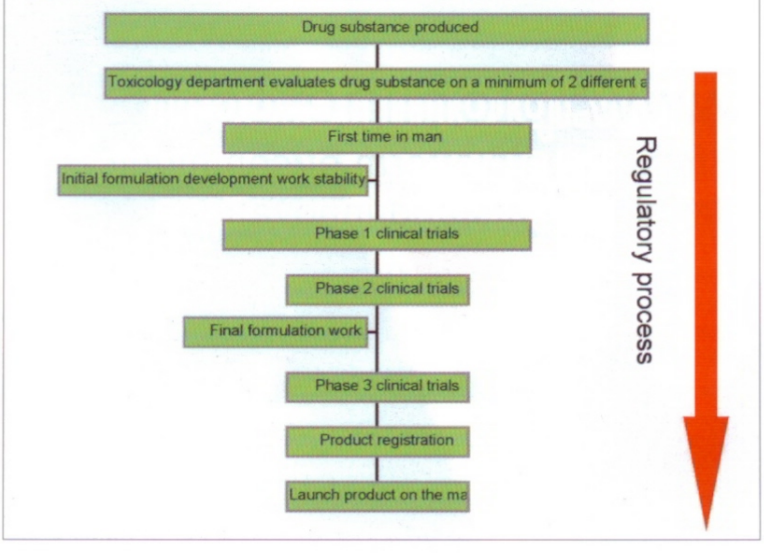
Figure 1. Schematic of the pharmaceutical drug development process.



candidate. A brief outline of the key development stages is given in Figure 1. An opportunity to speed up any of these stages will have a direct effect on the overall development time, resulting in the compound being introduced onto the market more quickly. Thus speeding up one or more of these stages is highly desirable.

Early stage formulation

A considerable amount of time is spent at the early stages of drug development preparing the product samples for testing. Early stage development often requires significant formulation effort at a time when the final drug form is undecided and this can be rate-limiting to the development process. For example, samples for pre-clinical and Phase I/II clinical trials may not be in the dose format of the final formulation, and an interim dose form is used to facilitate administration to both animals and humans. Many drug development scientists choose to use capsules during these early-stage studies, as they are flexible and represent a relatively inexpensive method of administering a drug. Unfortunately, the use of capsules does present some problems.

Capsules are relatively easy to fill if large volumes of powder are being dispensed. However, the amount of drug administered in these early trials is often less than 200mg and typically in the region of 0.5–100mg. In order to overcome this problem, the developer had – until recently – only two options from which to choose:

1. Add a suitable inert excipient (for example, lactose) to the drug product, produce a blend and fill the capsule using this bulked and blended powder. This would contain the desired dose, and have a large enough volume to be able to handle the product and fill the capsule with the desired level of accuracy.
2. Fill the capsules, using skilled operator(s), by weighing the required amount of pure drug into a capsule manually. Historically, this option has been limited to amounts of drug of 20mg or more, but with more potent materials coming through research, operators are now faced with extremely tedious weighing of even smaller quantities.

Both of these options are currently used, but both have their own drawbacks. In the case of Option 1, the addition of the excipient facilitates ease of drug/blend handling and filling. However, the blend needs to be manufactured, analytically tested, filled and tested, and then undergo stability trials to demonstrate that the excipient does not alter the chemistry of the active drug or increase its degradation (either immediately or over a period of time – often weeks or months). The blend cannot be prepared until sufficient drug is available as often several blends need to be produced before a batch with adequate homogeneity is manufactured. Early trials are intended to provide information about the drug, and the use of excipients that may not be used in the final formulation can be a "distraction" to data interpretation.

With Option 2, the skilled operator can manually weigh an amount of pure drug into a capsule. This is acceptable if the number of samples needed is low. If, however, larger numbers of samples are required, then the time to prepare these samples can be considerably longer. It is an arduous task – requiring a skilled operator to perform what is essentially a mundane task. If the weight required is low (for example, tens of milligrams or less), this filling process may take up to five minutes per capsule; furthermore, achievement of a desired weight within precise limits may lead to a significant attrition rate of capsules with weights outside the desired specification range. Even if only a small number of capsules is required – for example 100 – this can translate into a full day's work, not taking into account any 'rejects' that may occur.

Even with these options, some materials have proven difficult or even impossible to blend or fill by hand, because of their unusual powder characteristics.

Automation of powder handling

Recent advances in the application of automation to handling powder at the "micro-dose" level offer a significant improvement to this gloomy scenario. Whilst it has been possible to handle small amounts of powder for some time using gravimetric or volumetric methodologies, these have not been able to deliver the required accuracy, speed or precision at the micro-dose level. A recent entry into the marketplace – Xcelodose™ – uses a gravimetric filling method to fill drug powder into capsules and other solid dose containers. The system incorporates a novel metering technology in conjunction with sophisticated software; this controls the dosing by metering aliquots of powder from a dispensing head at speeds and accuracies previously thought to be impossible.

The core component is a gravimetric system with programmable levels of precision. The system uses a microbalance to provide an assurance of filled dose weights. A predictive control algorithm has been developed that reduces fill cycle-times to previously unobtainable levels. The predictive algorithm also enables the system to compensate for varying material characteristics, and even compensates for variability in the flow characteristic of the material in real time.

The Xcelodose™ system is available in two formats: semi-automated (the Xcelodose™ 120) and fully automated (the Xcelodose™ 600) (see Figure 2). The numbers refer to the throughput of filled capsules per hour that can be handled by the system.

Early stage development often requires significant formulation effort at a time when the final drug form is undecided ...

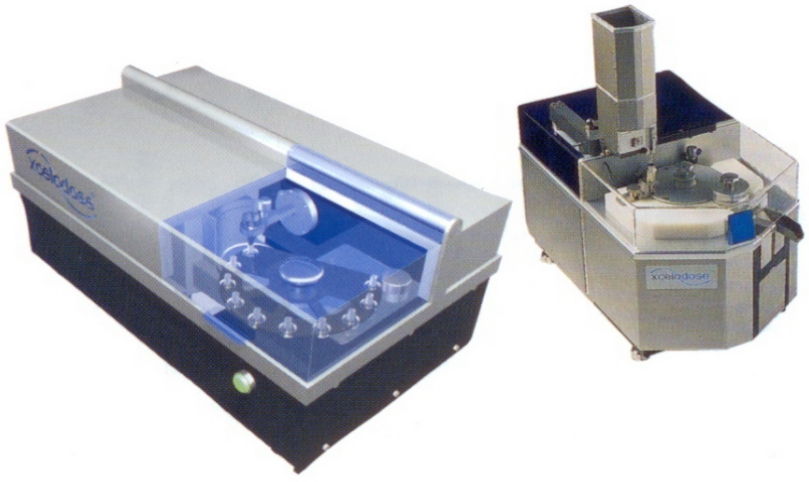


Figure 2. The Xcelodose™ a) 120 filling system and b) 600 filling system.

Performance and operating characteristics

Xcelodose™ has been rigorously tested using a wide range of materials having very different physical properties. These have included low bulk density powders to free-flowing crystalline materials, and cohesive, micronised and lyophilised powders. The system is capable of accurately dispensing powders that have a tendency to "ball" when handled and agitated. No segregation of powder into different particle sizes occurs. Experience in filling a variety of compounds and excipients has shown that the system is capable of handling a variety of particle sizes and weights, even at relative humidities as low as 5% RH for moisture-sensitive materials. Furthermore, novel drug delivery systems designed for the delivery of peptides and proteins may also be accurately and conveniently filled using the technology.

The system is capable of accurately dispensing powders that have a tendency to "ball" when handled and agitated

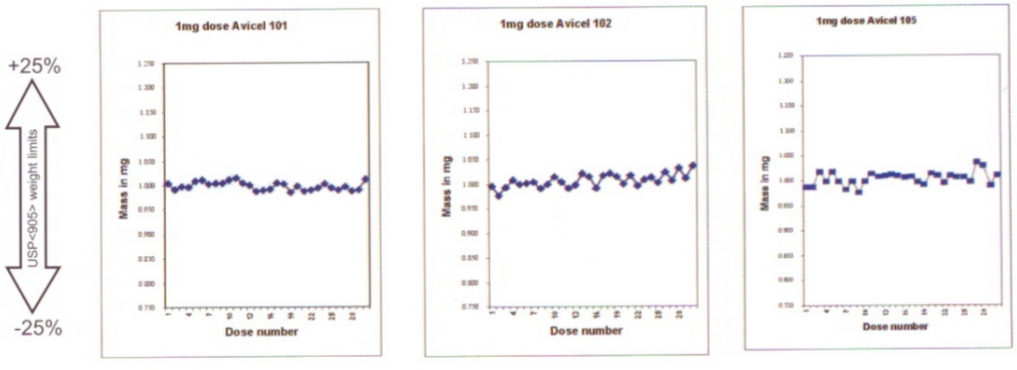
To exemplify the performance of Xcelodose™, a number of different grades of microcrystalline cellulose with different particle sizes (Avicel® 101, 102 and 105) and at a range of dispensing weights (1 and 100mg) were dispensed. The performance of the system when these contents were dispensed into 30 capsules is shown in Figures 3 and 4.

Xcelodose™ requires the selection of an optimum dispensing head to suit the particle properties and mass of the material being dispensed. In the example above, the sets of data on the various grades of material were generated using the same dispensing head – no attempt was made to select an optimum dispensing head based on the different particle sizes of the materials. In spite of this, the dispensing weight control was excellent, showing a maximum deviation from the nominal dispensed weight of only 4%, with a mean dispensed weight within 1% of target and RSDs in the range 0.84% to 1.41%.

The performance of the system in dispensing the same materials at a much higher weight of 100mg shows results comparable with those of the lower weight presented in Figure 3 – in terms of mean weight dispensed, maximum deviations from the nominal dispensed weight and RSDs. Clearly, the dispensing head selected for the dispensing of 100mg Avicel® 105 is regarded as optimum for this material, but the results obtained for each of the three grades were significantly better than the +/-25% USP limits by some considerable distance.

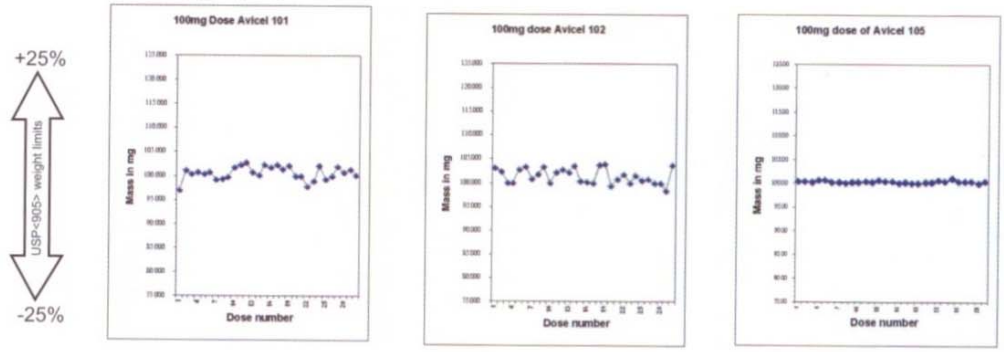
Microcrystalline cellulose is a free-flowing material and it was important to establish that the same levels of performance could be achieved with other less free-flowing, more cohesive powders. Figure 5 presents weight data for maize starch with a volume medium particle size of 13 microns at a capsule fill weight of 0.5mg. In this case, 900 capsules were filled in a single run. The mean weight dispensed was 0.502mg

Figure 3. Xcelodose™ dispensing microcrystalline cellulose at 1mg.



Avicel	101	102	105
D50	61um	109um	32um
Mean	1.00	1.01	1.00
RSD	0.84	1.28	1.41
High	1.02	1.04	1.04
Low	0.99	0.98	0.98

Microcrystalline cellulose



Avicel	101	102	105
D50	61um	109um	32um
Mean	100.55	101.40	100.18
RSD	1.39	0.99	0.81
High	102.68	103.80	101.01
Low	96.85	98.33	96.05

Microcrystalline cellulose

Figure 4. Xcelodose™ dispensing microcrystalline cellulose at 100mg.

with an RSD of 2.2%. Data for the "last" 376 capsules filled are presented graphically in the figure.

Also presented in Figure 5 is the dispensing time (right-hand axis) showing an average dispensing time of approximately two seconds. It should be noted that, for the last few capsules filled, the dispensing time was in excess of two seconds, and increased significantly for the last two capsules filled. This behaviour is characteristic of Xcelodose™ when the dispensing head is empty, with no material remaining in the dispensing head and hence no wastage. Because of the precision that can be achieved in filling very low weights, wastage of drug is kept to an absolute minimum. This is important when a drug is in short supply or is very expensive.

Graphic user interface

Each weighing is recorded into a secure read-only database, which is time and date "stamped". The data are then compared with the method settings, and a pass or fail flag is assigned to each weight. The system is designed to be compliant with 21CFR Part 11 in that data, once entered, cannot be altered and contains the facility for an electronic signature. The Graphic User Interface is designed to be user-friendly, and a variety of screens is available for both the input and output of information.

Two of the control screens available to the user are shown in Figure 6. The first screen presentation shows the set-up and "run initiation" process, and an ongoing graphic display of actual weight data achieved and the acceptance limits set. The second display presents the results obtained from individual capsules filled; it should be noted that "out of specification" capsules that are rejected are also highlighted on the display (in this example, capsule number 155).

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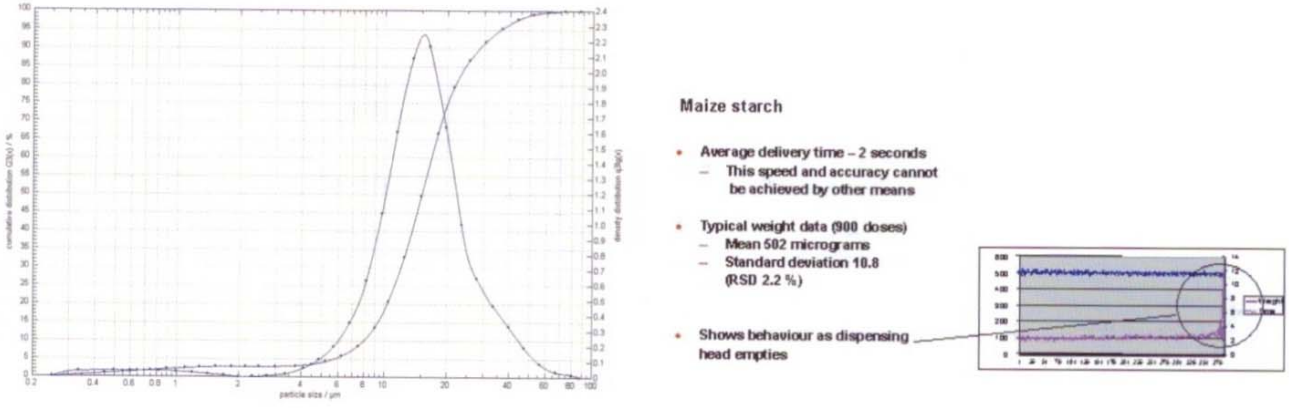
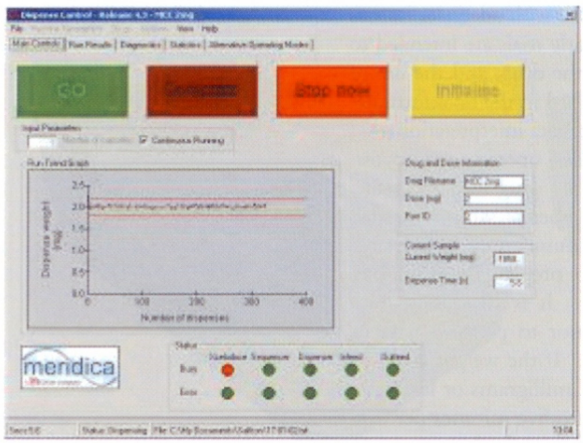


Figure 5. Xcelodose™ filling a cohesive powder – maize starch – at 0.5mg.



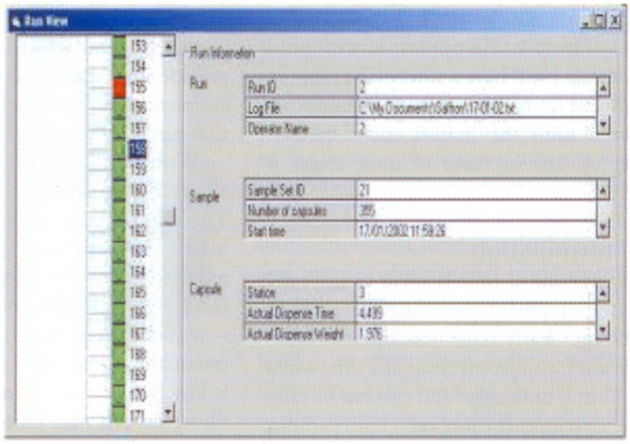


Figure 6. PC screen display.

The Xcelodose™ system is believed to be a good example of a technology that can offer a step-change in the way that early product development is carried out

The right-hand side of the display screen shows specific data relating to capsule number 158.

Conclusion

Reducing pharmaceutical development times has long been one of the key objectives for all pharmaceutical companies, as this can directly lead to additional revenue through early market entry and additional "in market" patent life. Most of the large pharmaceutical companies have carried out numerous major initiatives aimed at reducing the time to "first in man" and streamlining the overall drug development process. The objectives have been to make the process more efficient by shortening development time at each stage. These initiatives are, however, subject to "diminishing returns", as there is progressively less advantage that can be attained for each initiative taken. Furthermore, a successful initiative taken in one area of the development process can lead to additional pressures and demands in other areas.

Most approaches have focused on the *process* of drug product development and these have led to substantial efficiencies being gained; for example, commonality in the development process across different development centres within a company, and the "internationalisation" of product development. One area where substantial advantages may also be gained is through selected technology-based initiatives aimed at providing a "step-change" in the way product development activities are carried out in support of early clinical evaluation. These changes may not only bring about significant savings in resources and time, but may also offer considerable "quality" benefits in the process of data acquisition to support product development.

Such technology advances can only be exploited as and when they become available. The Xcelodose™ system is believed to be a good example of a technology that can offer a step-change in the way that early product development is carried out; no longer is it necessary to formulate drug compounds with bulking agents, lubricants and other product excipients for the preparation of early clinical trial supplies – thus rendering much drug product stability work and associated activities unnecessary. This clearly has promising implications for Phase I and II studies for both conventional and biotechnology products, and offers significant benefits downstream in terms of savings in development time and reduced time to market. With each day saved being valued at approximately $1 million of additional sales revenue, this becomes an extremely attractive proposition.

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Dr Ian J Smith is Chief Executive Officer of Meridica. He has almost 20 years' experience in the pharmaceutical and biotechnology industries. From the early 1980s until 1995, he operated as a senior manager in drug product development for a major pharmaceutical company, responsible for pharmaceutical technology and respiratory product developments.