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Evaluation of a Solid Dose Delivery Technology for Filling Capsules and Other Small Containment Systems with a Broad Range of Drug Substance and Carriers

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Abstract

Very small quantities of drug substance and other materials were filled directly into capsules and other small containment systems. This technology enables pharmaceutical developers to rethink the speed at which a molecule can enter clinical trials; a clinical trial batch can be produced without recourse to formulation activities and can be manufactured when only a few grams of drug has been produced, by the research chemists.

Introduction

Oral administration is the most desirable and convenient route for drug administration. It is frequently applied for screening compounds in Phase 1 trials and is the route of choice for Phase 2 for many therapeutic areas. The time and cost of preparing trial samples is dominated by the amount of work necessary to formulate the drug with multiple excipients and analytical work for dose uniformity and stability studies at different dose weights and concentrations.[1]

An innovative technology has been developed in our laboratories that is able to accurately fill solid dosage units with precise quantities of drug. This technology can be used for the preparation of clinical trial samples and dramatically reduces the requirement for supporting analytical and formulation work.

Method

Design of the delivery system: The Xcelodose technology provides accurate filling of pure drug in dry powder form directly into capsules and other small containment systems, at speeds and accuracies previously thought to be impossible. The core component is a gravimetric system with programmable levels of precision. The system (Figure 1) uses a microbalance to provide assurance of filled dose weights. A predictive control algorithm is used that reduces fill cycle times to previously unobtainable levels. The predictive algorithm also enables the system to allow for material characteristics, and even compensates for variability in the flow characteristic of the material in real time. The system has been evaluated using a wide range of typical pharmaceutical materials and drug substance.

Figure 1. The Xcelodose 600

The data described below were generated on the fully automated Xcelodose 600 and on the semi automated Xcelodose 120. The Xcelodose 600 is designed for automatic filling of up to 600 capsules per hour. The Xcelodose 120 can be customised to allow filling of other small containment systems.

Results and discussion

Test substances were selected to represent different physical properties of materials used in pharmaceutical products and to include a range of flow properties. Drug substance, excipients and blends have been dispensed using Xcelodose. The results are discussed below : Figure 2 and Table 1 illustrates the data obtained using microcrystalline cellulose. In each case 30 capsules were filled and at each fill weight and RSD of around 1% obtained. The flowability of microcrystalline cellulose is good[2], 1.41 g/s. The particle size distributions are illustrated in Figure 3.

Figure 2. Xcelodose dispensing a free flowing material of various particle size distributions

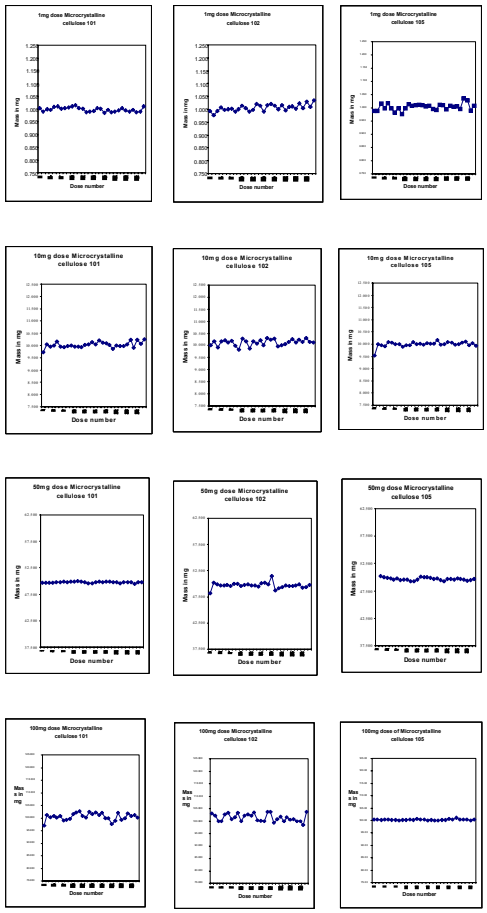
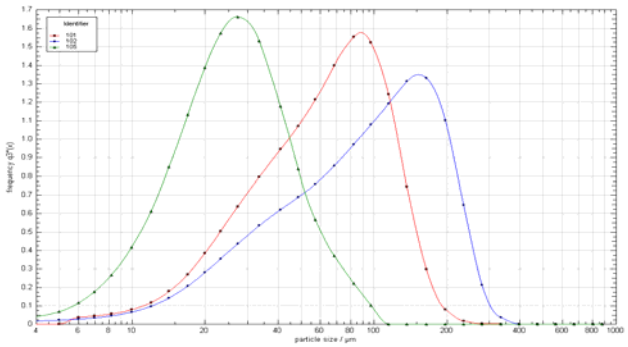


Table 1. Xcelodose dispensing a free flowing material of various particle size distributions

	Grade	101	102	105
Target Weight	D50	61µm	109 µm	32 µm
1mg	Mean	1.00	1.01	1.00
	RSD	0.84	1.28	1.41
10mg	Mean	10.03	10.13	10.00
	RSD	1.16	1.26	1.07
50mg	Mean	49.78	49.70	49.67
	RSD	0.25	1.05	0.50
100mg	Mean	100.55	101.40	100.18
	RSD	1.39	0.99	0.81

Figure 3. Microcrystalline cellulose particle size



Maize starch is usually regarded as a more difficult material to dispense. This material is described as cohesive with poor flow characteristics[2]. Nine hundred capsules were filled with maize starch with a target fill of 500µg. The median particle size (Figure 4) was around 15µm. The Xcelodose filled this material rapidly and with high accuracy and precision; the mean weight achieved was 500µg, RSD 2.2% (Figure 5).

Figure 4. The particle size distribution of the maize starch

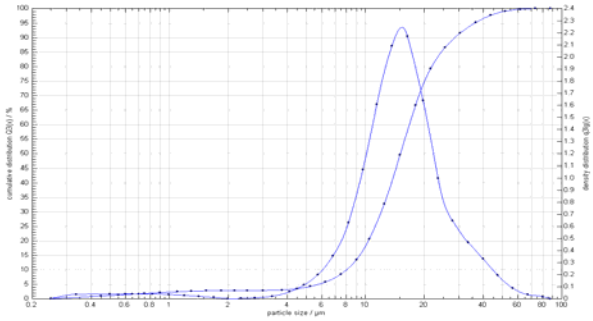
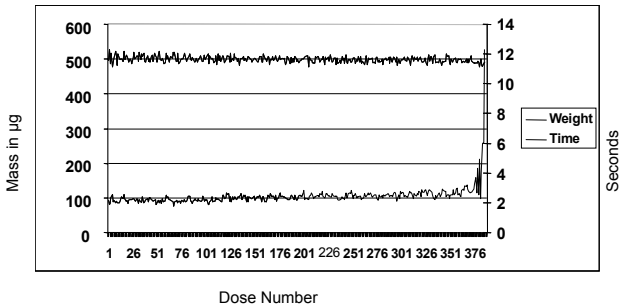


Figure 5. Capsules filled with 500µg of maize starch taking 2 seconds each to dispense. The last 400 capsules filled are illustrated.



The Xcelodose can dispense material leaving virtually no waste, the last capsule dispensed (Figure 5) results in 'time out' on dispensing time as by then the Xcelodose dispensing head is completely empty.

One example of typical small drug molecule is salbutamol sulphate, a widely used asthma therapy. The drug was dispensed as 1mg fill weight into thirty capsules. The drug has poor flow characteristics, as the crystals are non-uniform. The mean capsule fill weight achieved was 0.99mg, with a RSD of 1.6%. The particle size distribution of the salbutamol sulphate is shown in Figure 6 and the fill weight data are shown in Figure 7.

Figure 6. The particle size distribution of salbutamol sulphate

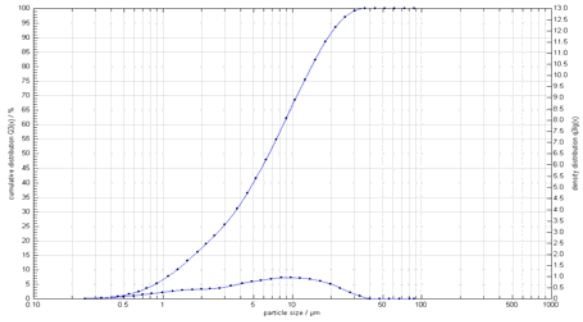
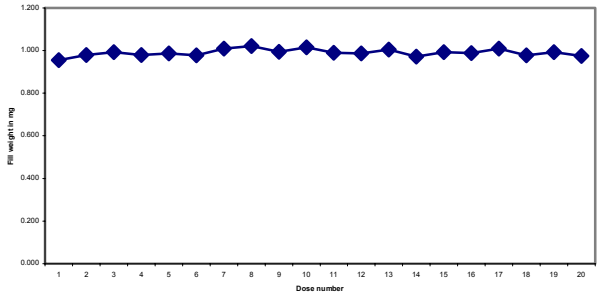


Figure 7. Xcelodose dispensing 1mg salbutamol sulphate as pure drug into capsules



The Xcelodose has also been used to successfully dispense a wide range of drug substance including both small molecules and proteins. The use of a specially designed dispensing head with innovative powder handling features has enabled the use of the Xcelodose technology with pure materials having widely differing flow characteristics.

Conclusions

Conventionally, it is not possible to fill pure drug into capsules or device cassettes at weights of less than about 20mg. At these low weights, careful drug powder preparation is required to ensure consistent powder flow behaviour. The Xcelodose technology allows the user to fill pure drug product at very low dose weights (0.1 mg upwards).

This technology means that it is no longer necessary to formulate the drug with bulking agents or lubricants to make filling possible and the associated stability work becomes unnecessary as drug can be directly dispensed into capsules. This has promising implications for Phase 1 and Phase 2 clinical studies of both conventional and biotechnology products.

Delivery systems designed for delivery of peptides and proteins may also be accurately and conveniently filled using this technology.

References

1. Gill. I, Edwards. D, Macmichael. B, Smith. I.J, Automating the preparation of test articles and clinical trial supplies. *European Pharmaceutical Contractor*, pp 36-40, Winter 2001.

2. Kibbe, AH. Handbook of Pharmaceutics Excipients, APhA 3rd Edition.

Note: Xcelodose® is a Trademark of Capsugel.