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Can Automated API Dose Dispensing be Accurate at 10 µg? An Analysis of Limiting Factors

David Beale[1], **Peter Woods**[1], **David Edwards**[2]

[1] GB Innomech Ltd,
[2] Capsugel, a division of Pfizer

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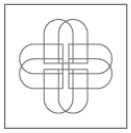

Can Automated API Dose Dispensing be Accurate at 10 µg? An Analysis of Limiting Factors

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Key words: micro-dosing, API dispensing, powder, accuracy, variability, dispensing limit

PURPOSE

Closed-loop micro-dosing using tapping, as embodied in the Xcelodose® precision powder micro-dosing system, is now well established for API dispensing and is qualified down to 100 µg. The physics of the process has been modeled and no fundamental limitation is known that prevents the technique being extended to lower dispensed amounts. The motivation for this work was to determine if a lower limit exists for effective use of this technology in practice, and what factors determine such a limit.

OBJECTIVES

Confirm the significant factors limiting repeatability and accuracy of automated powder dispensing, and consider their mitigation.

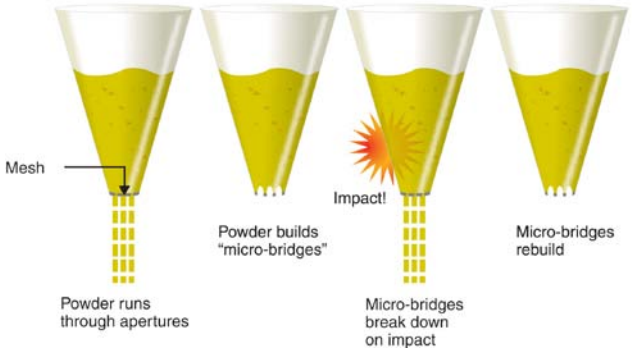
Quantify limitations on the accuracy of powder micro-dosing using closed loop dispensing as in Xcelodose systems arising from these factors.

Produce a means to estimate worst case tolerances on the dispensed amounts, for use in planning experiments and submissions.

Confirm by experiments the accuracy that can be achieved dispensing below 100µg, including the effect of optimising the Xcelodose system to address identified factors.

ANALYSIS

Powder is dispensed by a series of discrete taps each of which releases material from a hopper through a mesh (see diagram below).



The accuracy of dispensing is limited in two ways:
Variability in and quantization of the amount dispensed, arising from, for example:

- **Powder granularity**, which in turn might be affected by environmental factors, notably **Relative Humidity**.

- **Dispense head c**haracteristics.

- **Dispense method** parameters.

Uncertainty or error in the measurement of dispensed weight, arising from, for example:

- **Electrostatic** effects.
- **Rounding errors** in calculating dispensed weight.
- **Precision** of the microbalance.
- **Stability range** set for the microbalance.
- **Moisture absorption** or loss from capsules and powder.

As the dispensed amount is reduced, either one or both of these factors at some stage becomes large compared to the target amount, limiting the minimum weight that it is useful to try to dispense. Although a pass band can be set to automatically reject dispenses outside a tolerance limit, the process becomes very inefficient if the variability in dispensing exceeds the magnitude of the pass band. Furthermore, the variation in true weights in the accepted dispenses will be larger than is implied by the pass band since for example measurement error might cause an underweight dispense to be accepted.

- **Amount per tap:** Particle size and uniformity must be considered. A mean particle size above 10 microns may produce excessive variation in the amount dispensed per tap if the target amount is well under 100µg.

Even with a sufficiently finely divided powder, a dispense head (image of 3 dispense heads above) must be selected so that the amount released per tap is small compared to the target dose amount. In principle this is achieved by a suitably fine mesh, and so we constructed special dispense heads to test if this was a limiting factor in practice for dispenses down to 10µg.

- **Measurement error**: The effects of finite measurement resolution can be calculated and used to predict a range of variation for a given system in the absence of other factors. Systematic errors such as calibration error, buoyancy, and balance non-linearity in principle affect accuracy of weight measurement and were included in our calculations but are found not to be significant sources of error and do not become limiting with reducing dispensed amount.

The analysis included the following factors, with magnitudes corresponding to use of a Sartorius SE2 microbalance.

- **Machine pass band tolerance**: user defined, typically 10% of target weight. The machine uses the pass band as a parameter to control the dispense as well as a criterion for acceptance but this will

only contribute directly to variation if the amount dispensed per tap is of the same order.

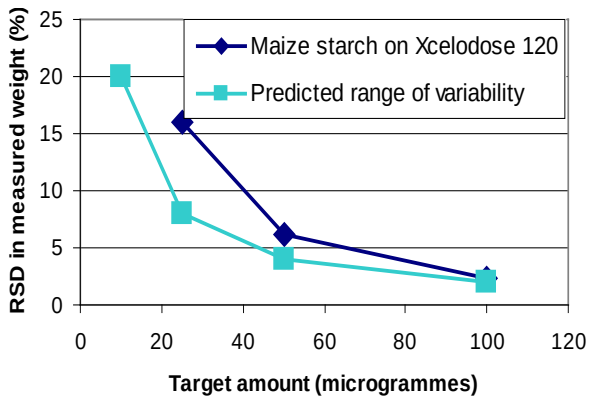
- **Stability range selected for balance**: user defined, typically 1 - 6µg. The stability range is the most critical parameter affecting repeatability of weighing. This can be reduced to 1µg or below provided the machine is properly isolated from ambient vibration.

- **Balance resolution**: 1 µg, can be reduced to 0.1µg. Rounding arising from the representation of weight in microgram increments an important contribution to the predicted error for low dispensed amounts.

- **Machine resolution**: 1µg, in principle could be reduced to 0.1µg.
- **Balance repeatability error**: 0.25µg.

- **Balance linearity error**: 0.4µg over 500mg.

- **Balance calibration error**: typically 12µg in 2000mg.



The graph above shows the predicted range of variation for an Xcelodose system set up with a 1µg stability range. The experimental data is from runs using the same parameters with 100% pass band.

EXPERIMENTS

Trials were carried out using Xcelodose 600S and Xcelodose 120S systems, each fitted with a Sartorius SE2 microbalance, both of which received modified versions of the control software during the course of this work.
A suitable choice of dispense head mesh was found to provide an average dose per tap 1% of target amount at all dispensed amounts with the powders used. During the trials electrostatic effects were initially a major factor affecting performance below 100µg. The introduction of a modified balance pan, made from stainless steel to give improved contact conduction, was found to resolve this problem.

RESULTS

Our calculations show the expected range of variability for a Xcelodose system using an SE2 microbalance displaying at a resolution of 1 with a stability criterion of 1µg is 3µg – a 30% error band for a 10µg dispense.
This range reduces to 2µg if the balance can operate at 0.1µg resolution, and if the entire system were to operate at that resolution so the stability criterion and pass band could be expressed as a fraction of a µg, the range of variability reduces to approximately 1.5µg. Other (non-calculable) sources of variation are then likely to dominate.

CONCLUSIONS

No lower limit in dispensed amount was found for the tapper/hopper system itself, but a practical lower limit is determined by measurement variability arising from the resolution and repeatability of the microbalance. The calculated minimum variability would only become significant at dispensed weights significantly lower than the machine specification of 100µg.

Practical enhancements to the machine together with an improved theoretical understanding of the limits to dispensing accuracy can lead to superior performance in the field, and open the door to even lower dispensed amounts becoming practical using the existing Xcelodose system technology.

REFERENCES

1. Aptuit (Edinburgh) Ltd. An assessment of the suitability of the Xcelodose 600 in the filling of blended products

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