

Investigation of Powder Changes on Delivery Characteristics from a Penn Century Dry Powder Insuflator™

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Summary

The Penn Century DP-4 Dry Powder Insuflator™ device has been used extensively to deliver micronised powder materials into the respiratory tract of various animal models. This work was conducted to investigate the practicality of delivering relatively large payloads from the device into a rat model, and to help understand how powder formulation could be used to maximise the efficiency and consistency of powder delivery.

A range of model spray-dried powders were tested, comprising: mannitol, and mannitol with 2.5%, 5%, 10% and 15% w/w L-leucine. Varying powder masses between 5 and 10mg of powder were loaded into the device, and emitted doses were determined. Significant variation was observed in delivered dose consistency between the formulations, with emitted dose increasing in line with the level of leucine added.

Background and Objectives

The Penn Century DP-4 Dry Powder Insuflator™ device has been used extensively to deliver micronised powder materials into the respiratory tract of various animal models (1). Despite this broad use, relatively little has been published on the characteristics of the delivered cloud that is generated during its use, especially as a function of higher doses. In most cases, only aerosol data from the subsequently employed dry powder inhaler platform for use in humans are published.

We intended to utilise the Dry Powder Insuflator for the delivery of a novel small molecule directed for systemic delivery at relatively high doses. Hence, we were concerned with regard to the uncertainty introduced by any variable state of the aerosol, uncertainty in the delivered dose, plus an uncertainty in the reproducibility of operation. Consequently, we report here the initial findings of a study conducted in order to understand the efficiency and level of variability in delivered dose of a model material from this device, and to design a powder platform that could maximise the efficiency and consistency of powder delivery to the rat model. This study is part of a larger project in which we are also looking at the de-agglomeration efficiency, and subsequent development of this platform to our compounds of interest.

Materials and Methods

The DP-4 Insufflator is a hand-operated polyetheretherketone pulmonary delivery device designed to produce a controlled bolus aerosol of fine particles from the end of a small-diameter delivery tube. The device opens in the middle providing a holding chamber that can be filled with a fixed amount of powder. A valve assembly prevents the powder sample from leaking from the holding chamber prior to actuation. At the exit from the device is a fine stainless steel needle that directs the bolus into the lungs of the model.

Actuation occurs by applying approximately 3ml of air to the device from a plastic syringe, compressed by hand. Dose delivered from the device was determined gravimetrically, by weight before and after actuation. The actual dose that can be held within the device is determined by the volume available, hence is a function of powder density.

Mannitol was selected as our model compound. It was spray dried using a, Buchi 190, Spray Dryer (Buchi, Switzerland) with varying percentages of the amino acid L-leucine, keeping the solids loading fixed (5% w/v of water), using conditions previously seen to provide particles of approximately 5 micron median diameter. The

leucine content was selected as 0% (no leucine), 2.5%, 5%, 10%, and 15% leucine to mannitol w/w. Leucine has long been known to aid in aerosolisation when present on the surface of drug particles either by mechanical addition or by co-spray drying (2). Leucine is believed to migrate to particle surfaces, change surface chemistry and particle morphology which may be beneficial to dispersion (3,4).

Powder masses of approximately 5 and 10mg of powder were loaded into the device. These were relatively high powder masses compared with those previously reported for the DP-4, but were of the anticipated range of load required in our subsequent studies. Emitted dose was calculated by shot weight. Each measurement was repeated 3 times, with mean and standard deviation values calculated.

The mean bulk aerated density of each of the spray dried mannitol powders was also assessed. Bulk density is not only an important consideration when anticipating powder cohesiveness and flow (5), but is also an important consideration when the powder mass that can be loaded into a device is limited by volume available in a holding/metering chamber. Mean tap densities were evaluated (n=3) in a calibrated measuring cylinder. Tap density was determined using a tapping machine (Autotap, Quantachrome Instruments) by standard tap procedure until no further compaction was obtained.

Results and Discussion

Figure 1 presents the percentage delivered dose from the DP-4 device, for approximately a 5mg powder loading of each of the spray dried mannitol and mannitol-leucine powders. Similarly, Figure 2 presents the percentage delivered dose from the DP-4 device, for approximately a 10mg powder loading of each of the spray dried powders. The values plotted were calculated as a percentage of the mass of powder loaded into the holding chamber, and as an average of 3 determinations. Standard deviations are also plotted to illustrate the variation in each case

As can be seen from this initial study, we were only able to achieve emptying efficiency of a 5 or 10mg load of a fine mannitol powder of around 10%. This represents a very high loading for the DP-4 device, and it appears compounded by the cohesivity of the mannitol microparticles produced. However, there was a significant improvement in percentage of emitted dose with the addition of leucine. Even at 2.5% w/w, the leucine makes a substantial change to the DP-4 device emptying efficiency for both doses, and at 5% addition, emptying was in excess of 50% in both 5 and 10mg loading.

In general it appears that increasing amounts of leucine may improve both the efficiency of device emptying, as well as the reproducibility. However, we found that in practice the reproducibility of the device emptying was also dependant on operator variation, and at 10mg fill, 15% w/w leucine a high variance in emptying was observed. Because the operation is driven by a manual plunge of the syringe, this was considered to be a potential source of variability that was difficult to control. We note here, that in the context of subsequent *in vivo* studies, this control is likely to be more difficult to ensure due to the additional complexity of animal handling.

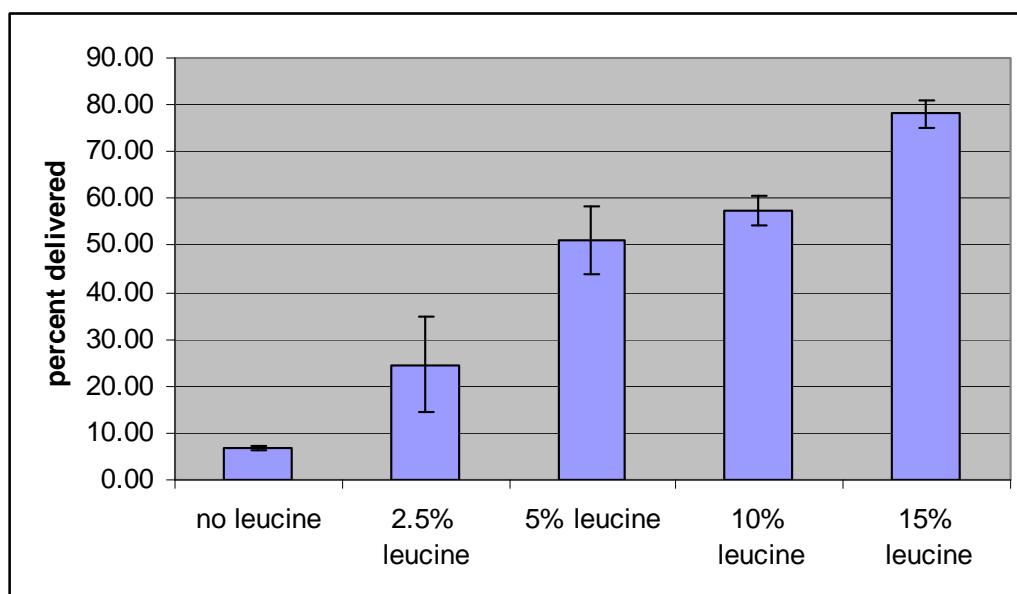


Figure 1: Percentage of powder mass dose emitted, from approximately 5mg fill

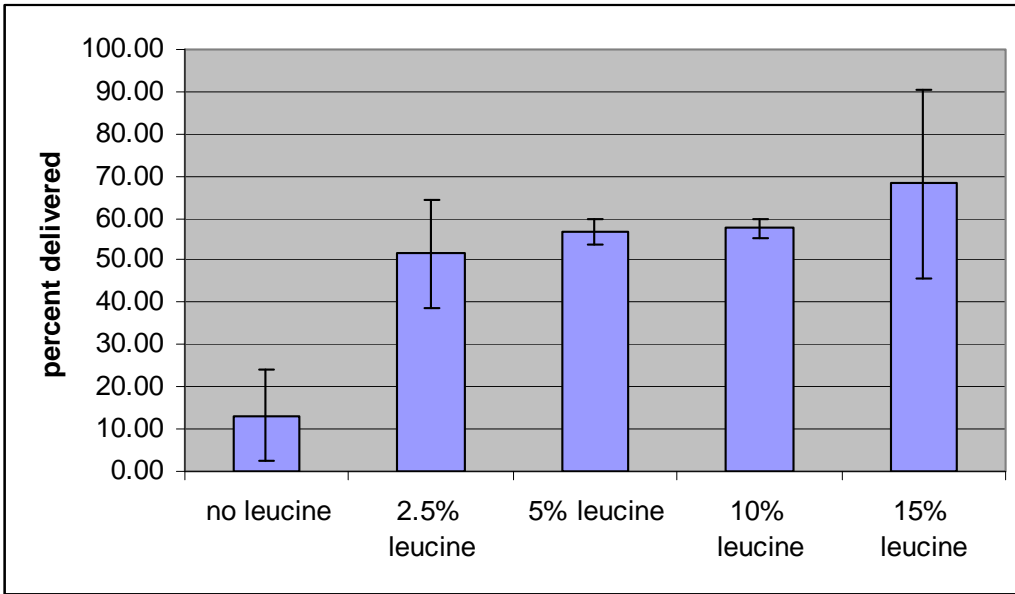


Figure 2: Percentage of powder mass dose emitted, from approximately 10mg fill

The tapped density values for these powders are presented in Figure 3.

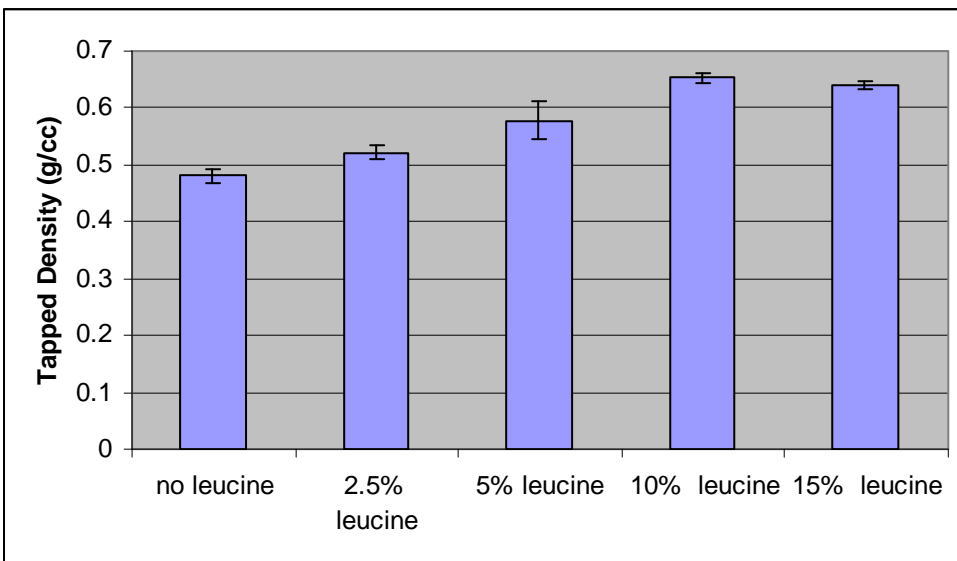


Figure 3: Tapped density measurement for spray dried powders

It is interesting to note from this data that as increasing leucine is added to the mannitol, the tapped density increased from a mean of 0.48g/cc for pure mannitol up to 0.64g/cc for mannitol with 15% w/w leucine. This appears in contrast to previously observed effects that the addition of increased leucine appeared to create an increased tendency to more highly corrugated and apparently increasingly porous particles, which might be expected to decrease the bulk density of such spray-dried particles. We speculate that if increased addition of leucine decreases the envelope density of individual particles, this effect may be countered by the decrease in cohesion between particles, leading to more efficient packing, hence an increased tap density. In the next phase of this work, we will examine these materials under SEM, and investigate the particle surface chemical and physical properties, to establish the nature of such interactions.

Conclusions

Significant variation was observed in the delivered dose consistency as a function of leucine content. Clearly this study indicates the need to optimise powder characteristics if doses of 5mg and above are intended to be delivered in an in vivo study. It is interesting to note the beneficial effect that adding leucine via a co-spray dried route has on our mannitol model powder. This study also shows an interesting increase in tapped density of the leucine containing powder, consistent with the leucine reducing surface cohesivity of the powder.

In our subsequent work we will also investigate the de-agglomeration performance of these powders from the device, given that the state of powder de-agglomeration may influence the pharmacokinetics of drug uptake from any in vivo inhalation studies.

Acknowledgements

Sangita Agarwal was supported by an Australian Government Endeavour Award.

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