

Evaluating Impact of Inhaled Particle Size on PK Profile of AZD1 Using The PreciseInhale

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Abstract

For inhalation toxicology studies, it is known that individual batch to batch variance can have an undesired outcome on dosimetry, exposure and tolerability. One important factor for consideration when selecting dose levels, if a change in batch is required, is particle size. To fully investigate this before embarking on a chronic dog toxicology inhalation study with the novel glucocorticoid-receptor agonist AZ1 (iSGRM), an experiment was conducted utilizing the PreciseInhale aerosol generator. The design of this experiment was to evaluate the impact on systemic exposure following the inhalation administration of the same test substance but with two differing primary particle sizes, in the beagle dog. The PreciseInhale is a novel inhalation R&D platform which was selected for this experiment due to the quick set up, short characterization time, and for the ability to use small precise amounts of test item compared to the traditional method of blade scraping aerosol generator. The PreciseInhale also has an advanced computer control program along with an inbuilt Fleisch pneumotachograph, which allows for a controlled delivered dose, ideal for this type of investigation. The results showed an overlap based on mean systemic exposure to AZ1 indicating no major deviations between the two batches. Using this data, dose levels could be selected with confidence before moving into the toxicology study, reducing the risk for tolerability limitations in animals inherent with this class of drugs. This study provided a precise approach to assess potential for batch variation, removing some of the possible variance in other exposure systems

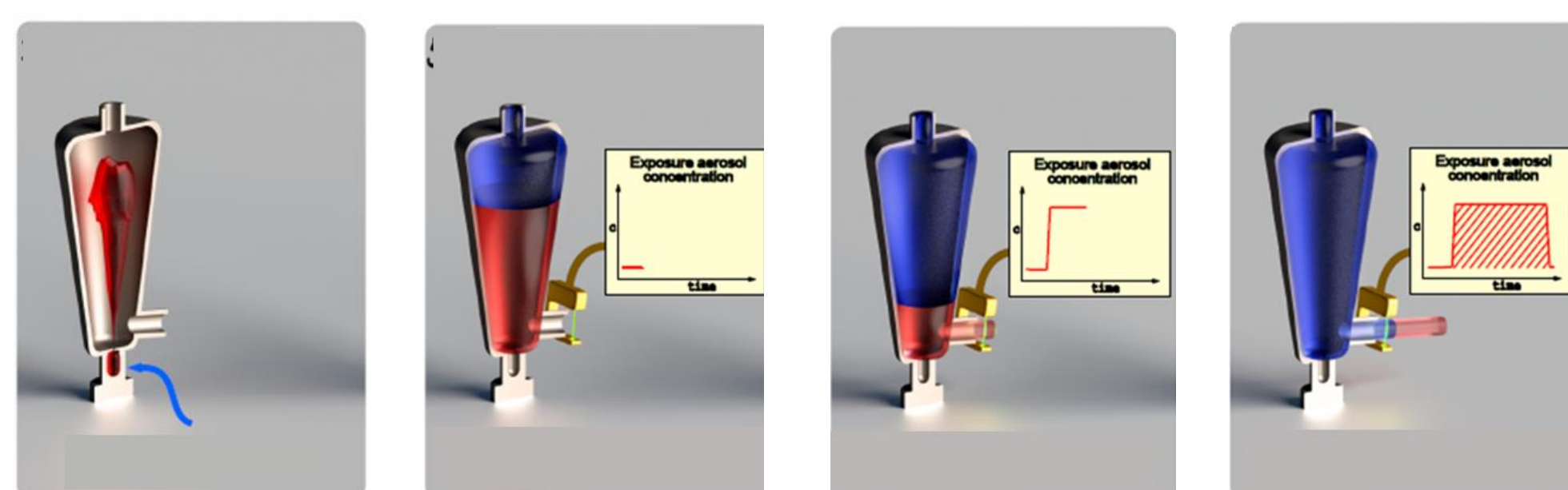
Introduction

For pharmacological agents with a distinct profile of dose limiting effects, relatively small variations in exposure can have a significant impact on tolerability. In inhalation studies it is known that batch differences in particle size distribution can influence exposure, hence this is an important factor to consider when selecting doses for inhalation toxicology studies. In one program of work using a glucocorticoid-receptor agonist a batch change was required moving from one toxicology investigation to another where the primary particle size had been altered. A critical consideration in this instance is, would the effect of particle size modification result in a change in pharmacokinetic parameters, when compared to the previous batch, resulting in an undesirable dose, creating animal welfare concerns and possibly jeopardizing the project. To investigate this fully before embarking on a chronic dog inhalation toxicology study an investigation was conducted using the PreciseInhale aerosol generator and investigating the effect on systemic exposure in the beagle dog following inhalation of the same compound at similar doses but with different primary particle sizes.

The PreciseInhale

The PreciseInhale is a unique aerosol generation R&D platform that is able to generate a dry powder aerosol in a free flowing state thereby removing the need to compact the dry powder inhalation substance which can so often lead to aerosol concentration variability. The PreciseInhale has other unique attributes which made it ideal for this investigation such as an inbuilt Fleisch pneumotachograph to monitor the dogs tidal volume and breathing frequency, quick to set up and characterize the aerosol, very little test item wastage due to high generation efficiency and no residual dead space volume as is common place with other commercial dry powder aerosol generators.

Figure 1 The PreciseInhale R&D Platform



- 1) High pressure air aerosolises powder into a plume
- 2) Aerosol settles into holding chamber and controlled air flow "pushes" API past a real time aerosol monitor
- 3) Real time aerosol concentration and dose logging.
- 4) Precise exposure control

Figure 1 The left image shows the PreciseInhale aerosol generator, and on the right the images display the mode of aerosol generation. Whereby high pressure air pushes a bolus of powder into the holding chamber, then a controlled flow of air pushes the aerosol down past a Casella Microdust real time aerosol monitor which then precisely controls the exposure.

Results

In vitro characterisation

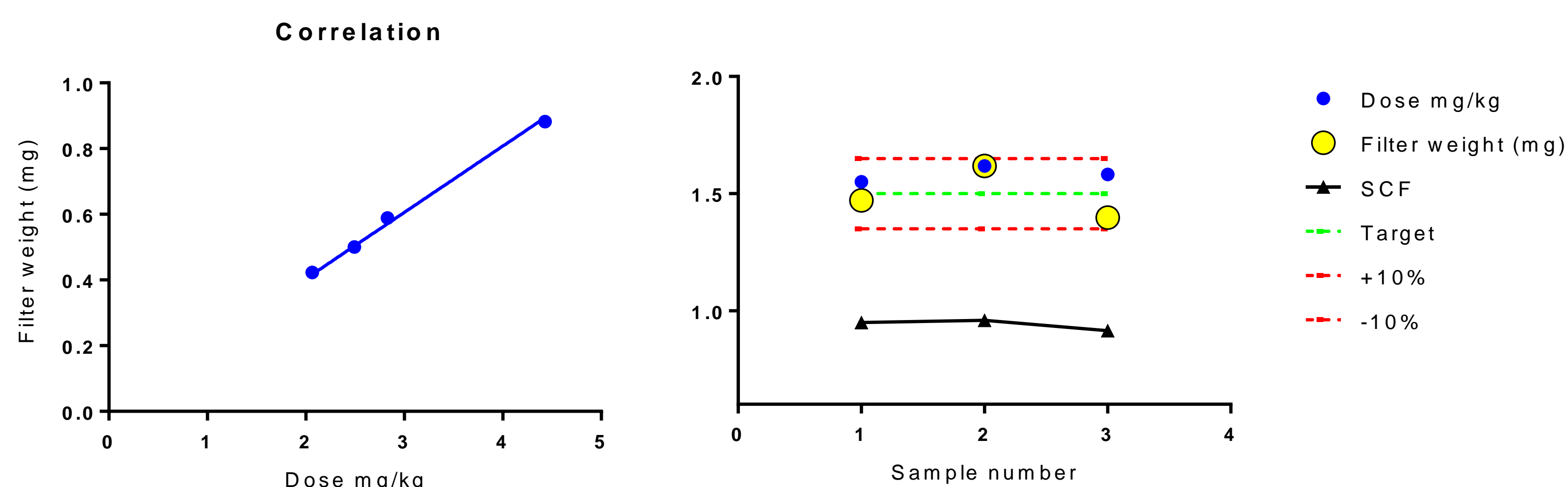


Figure 2 A

Figure 2 B

Figure 2 shows the results from the *in vitro* characterisation performed in advance of the *in vivo* exposure. Figure 2a demonstrates the correlation between the dose calculated by the real time aerosol monitor and the amount of test item collected of a 25 mm glass fiber filter. Results indicated a close correlation with a R squared value of 0.1. This data provided a consistent substance correlation factor which in turn led to the data generated in figure 2b which demonstrates the consistency between individual doses when a target is set and the PreciseInhale administers the dose.

In vivo Results

Figure 3 Results Table Showing Achieved Dose and Exposure Data

Batch 1				Batch 2			
Dose (mg/kg)	C _{max} (nmol/L)	t _{max} (hr)	AUC (nmol*h/L)	Dose (mg/kg)	C _{max} (nmol/L)	t _{max} (hr)	AUC (nmol*h/L)
1.52	9,02	0,25	99,9	1.45	7,20	0,17	89,8

Figure 3 shows the mean achieved doses and the systemic exposure data following one single exposure of batch 1 and one single exposure of batch 2 in n=3 beagle dogs. On comparison with historical data in the dog, when exposed to AZ1 the data generated indicated an acceptable level of variance in mean systemic exposure values and a consistency between exposures with only a 5% difference in achieved doses. This can also be observed in figure 4 below, which shows the mean PK profile between the two different particle sizes. The results from this experiment demonstrated a similarity in mean value PK data indicating no major deviations between batches. With this data dose levels can be selected with confidence moving into the 9 month toxicology study, reducing the risk for tolerability limitations inherent with this class of drugs

Figure 4

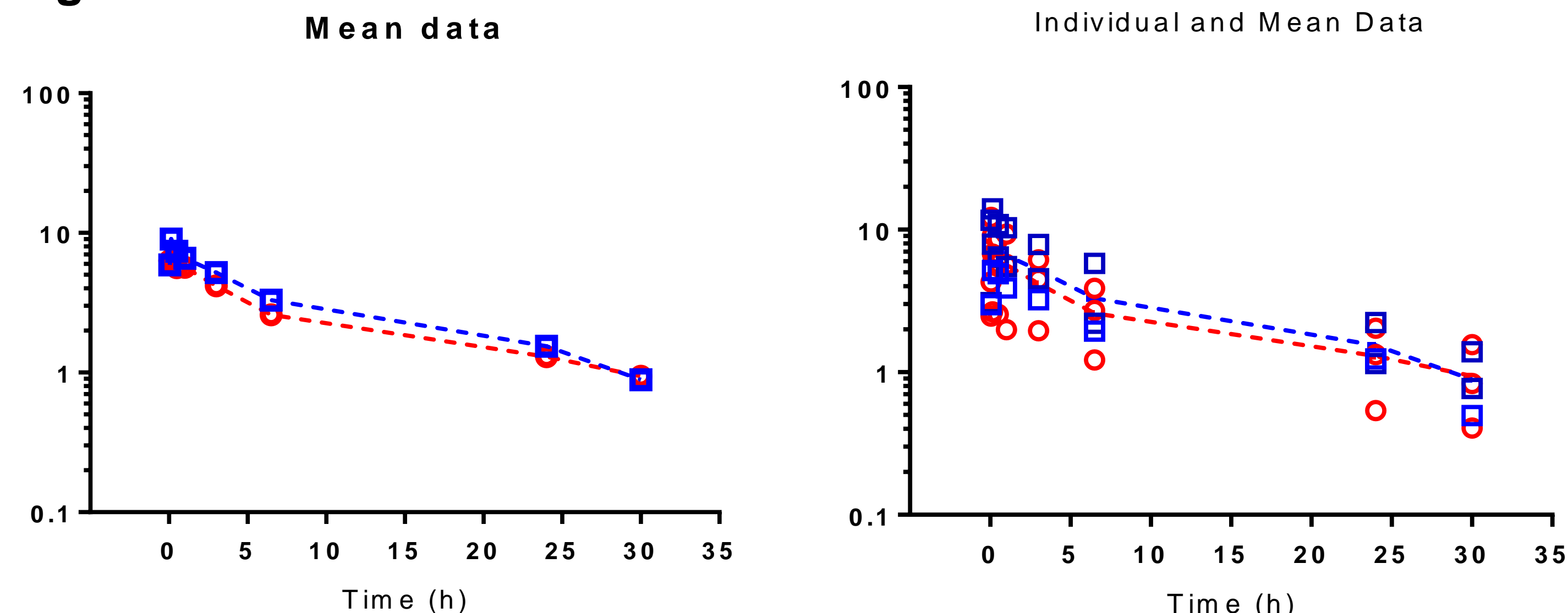


Figure 4 Pharmacokinetic profiles; mean PK profile between the two different particle sizes. Data demonstrated a similarity in mean PK data indicating no major deviations between batches

Conclusions

The PreciseInhale was selected for this experiment due to its unique operating principles that would help to achieve a precise dose to investigate the particle size difference in a given compound. With similarity seen in achieved doses and an acceptable level of variance in mean systemic exposure parameters it was demonstrated that the PreciseInhale was precise enough to perform this investigation and offers a unique possibility in further exploring the impact of particle size on systemic exposure following inhaled dosing. Using this data, dose levels could be selected with confidence before moving into the toxicology study, reducing the risk for tolerability limitations in animals inherent with this class of drugs. This study provided a precise approach to assess potential for batch variation, removing some of the possible variance often seen in other exposure systems

References

All data taken from AstraZeneca studies

