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Clickhaler® dry powder inhaler: focussed in vitro proof of principle evaluation of a new chemical entity for asthma

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Abstract

A new chemical entity (NCE) was evaluated in the Clickhaler® (Innovata Biomed Ltd.) dry powder inhaler, a reservoir-based multidose delivery system. The standard device metering system was modified to handle higher doses (nominally 20 mm^3 of lactose based blend). The micronized drug was formulated at 12.5% w/w in lactose monohydrate (Pharmatose 325M, DMV) equivalent to a nominal dose of approximately 1 mg. Delivered shot weight (mg of blend) and emitted dose (μg drug) averaged 7.4 mg and 905 μg, respectively, and were consistent (within ± 20 to 25% of mean) through the life of the inhaler. The fine particle fraction (FPF) (Andersen cascade impactor) was typically 60%. A short stability study (i.e. 3 months at room temperature, 53 or 75% RH, unpacked) showed that the in vitro performance was maintained. The results of these studies provide in vitro proof of principle for this novel drug/device combination.

Keywords: Dry powder inhaler; Asthma; Aerosol

Pressurised metered dose inhalers (pMDIs) are widely used for the treatment of airway diseases. Traditionally, these devices used chlorofluorocarbon (CFC) gases as propellants, however, concern over the environmental impact of these gases resulted in the phase-out of CFCs as pMDI propellants (The Montreal Protocol, 1994). Although development programs to replace CFC propellants with hydrofluoroalkane (HFA) propellants have been pursued, there are occasions where a pMDI may not be the dosage form of choice, for example, in pediatric and elderly populations where patients may not coordinate actuation of the device with the inspiratory maneuver. Thus, the industry has also driven the development of propellant-free, breath-actuated dry powder inhalation systems.

The pulmonary route has become widely used and is under intense investigation for the local or systemic delivery of small molecules, proteins and peptides (Ganderton, 1997). In many cases, new chemical entity (NCE) development programs center on dry powder technology and have contributed to the evolution of novel delivery sys-

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tems. The Clickhaler® (Innovata Biomed Ltd.) is a novel dry powder inhaler that delivers multiple doses from a drug reservoir. In addition to the advantage of requiring no coordination between actuation and inhalation, the Clickhaler offers other design advantages including a metering system that prevents accidental multiple dosing, a dose counter, an end of life lock-out system, different metering cones to provide a range of doses, and a conventional inhaler appearance (Parry-Billings et al., 1999). A number of different reservoir dry powder inhalers are available for which in vitro aerosol performance has been reported including the more established Turbuhaler device (Meakin et al., 1995) and new devices such as the Twisthaler (Yang et al., 2001).

The discovery of new pathways for the treatment of respiratory diseases has accelerated the development of NCEs. Particularly, asthma has been the target of intense research efforts. Anti-leukotrienes (montelukast, for example) is a new class of compound that has been developed to aid in the treatment of the disease. The complexity of asthma warrants the need for novel disease modifying drugs. The compound tested has shown pharmacological activity in preclinical models of pulmonary diseases. It is a drug candidate with a molecular weight approximately 700. From a physicochemical point of view, it is an X-ray amorphous material with a high glass transition temperature. It has undergone air-attrition milling to produce micron size particles suitable for inhalation.

The goal of the study was to establish the feasibility of using a NCE/lactose blend in the Clickhaler as a means of producing an acceptable high-quality aerosol. Specifically, after an initial formulation screening to identify an acceptable drug loading, the in vitro aerosol performance of the blend was evaluated from the device. Additionally, a short-term stability study was performed on unpacked inhalers where the same in vitro performance parameters were evaluated.

Design of the Clickhaler can be modified to accommodate a range of doses. The dosing mechanism consists of a metering cone, which sits below a reservoir of drug. The cone has a series of metering dimples on its surface, which are filled with drug blend from the reservoir. Different doses can be achieved by altering the volume of the dimples on the cone (Fig. 1). For the study described here, the standard device was modified to handle higher doses (i.e. nominally 20 mm^3 of blend).

The micronized drug had a mean diameter of 3.5 μm with 90% less than 5 μm as determined with a laser diffraction Microtrac particle size analyzer (Honeywell, Montgomeryville, Pennsylvania) using a particle-in-liquid dispersion technique. A blend of the compound was prepared at 12.5% w/w in lactose monohydrate (Pharmatose 325M, DMV, Veghel, The Netherlands) corresponding to a nominal dose of approximately 1 mg. This blend concentration was evaluated further as it represented an optimal drug loading to achieve the anticipated dosing regimen for this particular drug whilst not compromising formulation characteristics. The blend was prepared using a Turbula mixer (Bachofen, Basel, Switzerland) and an appropriately sized container filled to approximately 50% volume. Previous experiments showed that adequate homogeneity was achieved after 40 min at 46 rpm. The blends were stored at ambient conditions in sealed amber glass bottles prior to use.

The devices were filled by hand and tested for shot weight, emitted dose, and aerodynamic particle size distribution. The devices were evaluated initially and then at regular intervals for up to 3 months after exposures to different relative humidities (i.e. desiccator/saturated salt solution to produce 53 or 75% relative humidity at room temperature) in an unpacked condition. At each time point, the experiments were conducted with at least two different devices.

The delivered shot weight was determined by weight loss following actuation of the device. The device was tared, a 'shot' was wasted in an appropriate collecting unit and the device was re-weighed to obtain the delivered shot weight.

The emitted dose was verified according to the test described in the United States Pharmacopoeia (USP). The devices were tested at the beginning, middle and end of life using apparatus B (Dosage Unit Sampling Apparatus—DUSA) at a flow rate of 50 l/min. No 'priming' shots were included in

the testing regimen. This flow rate was selected after it was shown to produce a pressure drop of approximately 4 kPa across the inhaler (Pharmacopeial Forum, 1998). The dose was collected from the sampling tube and assayed using UV-spectroscopy at 256 nm after dilution in methanol.

The aerodynamic particle size distribution was also determined according to a test described in the USP. The Andersen cascade impactor (Apparatus 3) was used to evaluate the in vitro respirable portion of the aerosol generated by the device. Typically, this value is defined as the portion of particles having an aerodynamic diameter less than 4.7 μm and is usually quoted as the respirable fraction (RF) or fine particle fraction (FPF). It is the percentage of the emitted dose with particles having an aerodynamic diameter less than plate 2 in the Andersen cascade impactor (nominal cut-off at 4.7 μm). The material was collected from each plate and assayed using UV-spectroscopy as described previously. The impactor was operated at 60 l/min corresponding to approximately 4 kPa across the

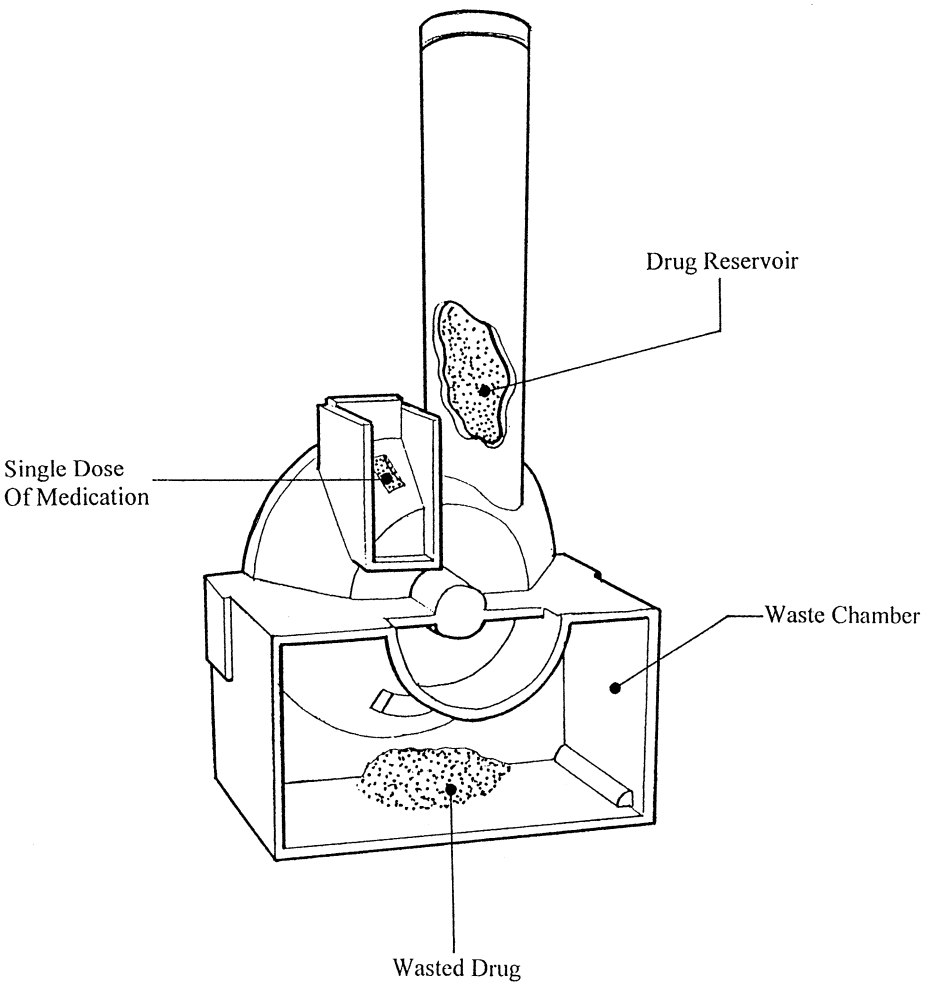

Fig. 1. A detailed view of the Clickhaler metering cone. Powder blend is stored in the cyclindrical reservoir above the metering cone. Single doses are metered by the 'cups' on the surface of the cone. On actuation of the device, a single dose is moved via rotation of the cone from under the reservoir to the inhalation passage. If the patient inadvertently does not inhale, drug is carried away to the waste chamber to prevent double dosing.

Table 1
Initial data for delivered shot weight, emitted dose, and FPF

	Delivered shot weight (mg)	Emitted dose (μg)	FPF (%)
Mean	7.4	905	59.3
S.D.	0.6	99	2.1
R.S.D. (%)	8.6	10.9	3.0

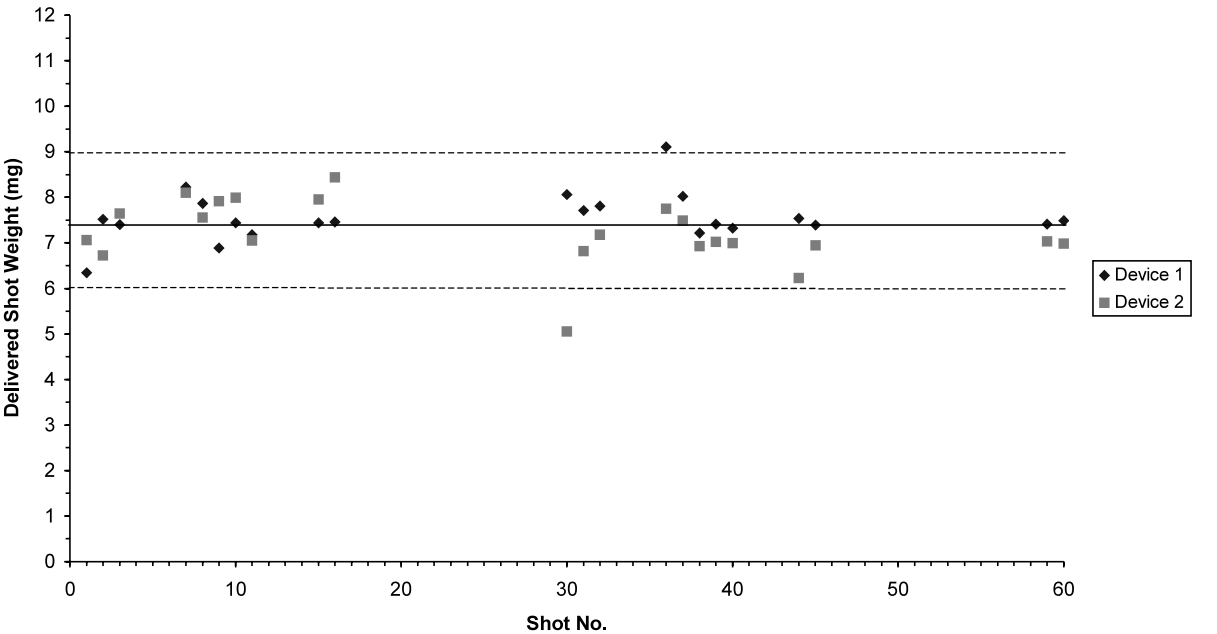

Fig. 2. Delivered shot weight data through the life of the device at the initial time point where the solid line represents the average and the dashed lines represent variations of $\pm 20\%$ ($n = 2$ devices, 22 shots per device).

device and the impaction plates were coated with 316 Silicone Release Spray (Dow Corning, Midland, Michigan).

Moisture content was measured using a coulometric Karl Fischer technique.

Table 1 gives a summary of the data for delivered shot weight, emitted dose and FPF. A mean delivered shot weight of 7.4 ± 0.6 mg with a relative standard deviation (R.S.D.) of 8.6% was obtained during this initial testing. Fig. 2 illustrates the shot weight data through the life of the device. From these data it is clear that most of the delivered shot weights are within 20% of the mean. A mean emitted dose of 905 ± 99 μg was achieved and the results given in Fig. 3 show that the emitted dose is maintained from the beginning through to the end of the device with all except one result within 25% of the mean. It appears that a high FPF can be achieved with mean FPF at baseline of $59.3 \pm 2.1\%$. This FPF value is higher than those usually achieved using this device and simple, non-proprietary formulation approaches (Fukunaga et al., 2000) but in line with data using proprietary formulation technology (Ostrander et al., 2000).

The in vitro performance data at the initial time point were encouraging, therefore, further data were generated to assess the performances of the product as a function of time and environmental conditions. Table 2 gives a summary of the delivered shot weight data after exposure to 53 and 75% relative humidity for up to 3 months in an

unpacked condition. It can be observed that the delivered shot weight remains unchanged after 3 months storage at both 53 and 75% relative humidity. Further to this, the results for emitted dose were also maintained at both study conditions. Fig. 4 illustrates that the mean emitted dose through life is unchanged by the stability conditions. Fig. 5 gives the results for FPF after storage. The results indicate that the high RF observed during the initial experiment is maintained for up to 3 months. It can also be seen that the amount of drug deposited on each plate is comparable throughout the study indicating that the profile of the particle size distribution of the aerosol cloud is unchanged by the environmental conditions (Fig. 6).

The results of an evaluation of moisture content support these data and indicate marginal increases in the percent moisture measured in each sample (Table 3). Storage at either 53 or 75% relative humidity in an unpacked condition does not appear to alter any of the key in vitro performance parameters of this drug/device combination.

A feasibility study has been described which demonstrates an in vitro proof of principle using

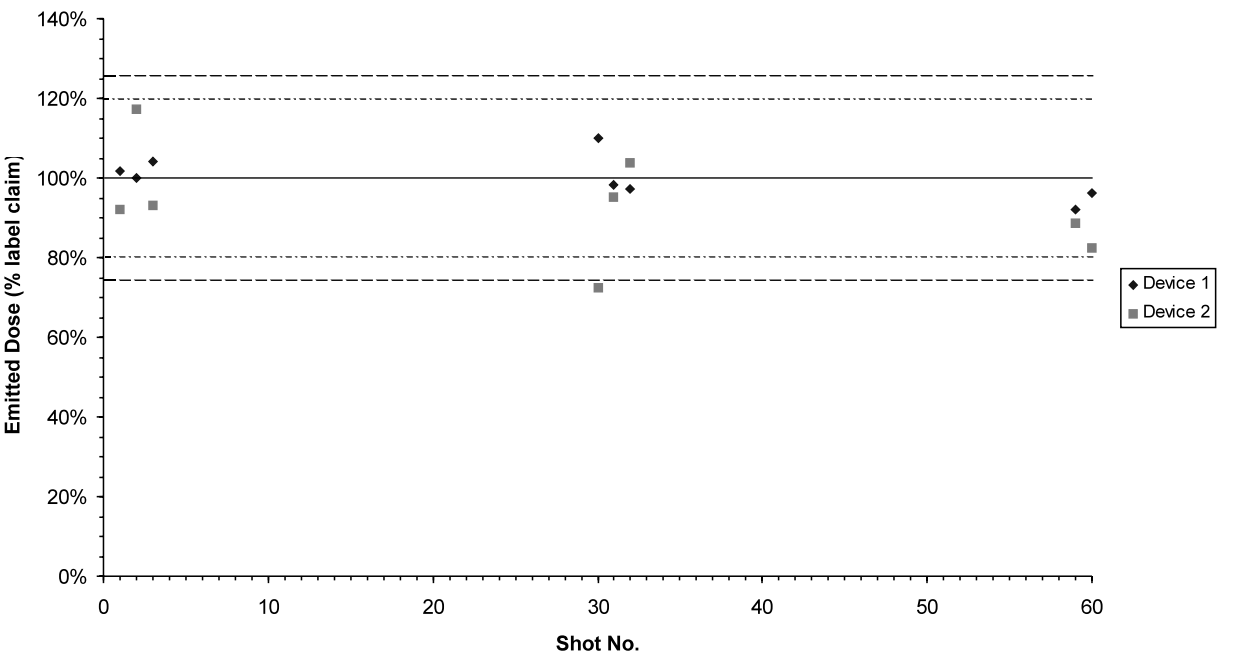

Fig. 3. Emitted dose data through the life of the device at the initial time point where the solid line represents the average, the dash–dot and long-dash lines represent variations of ± 20 and 25%, respectively ($n = 2$ devices, eight shots per device).

Table 2
Stability data for delivered shot weight

	Initial	53% RH		75% RH	
		1 month	3 months	1 month	3 months
Mean (mg)	7.6	7.4	7.9	7.8	8.2
S.D.	0.6	0.5	0.3	0.4	0.4
R.S.D. (%)	8.6	6.1	4.2	4.5	5.0

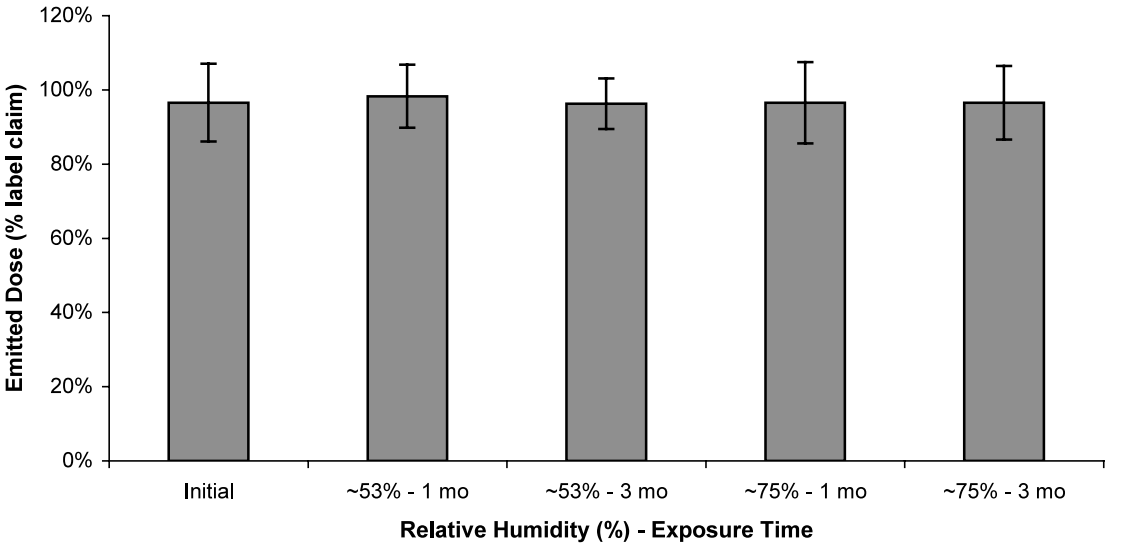

Fig. 4. The effect of storage at different relative humidity on emitted dose (percent label claim) where the error bars represent standard deviations ($n = 2$ devices per time point/condition).

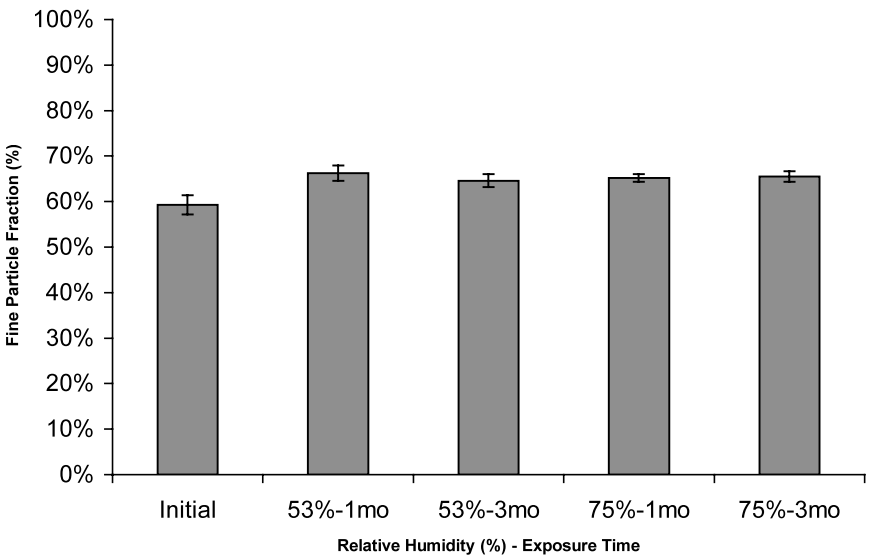

Fig. 5. The effect of storage at different relative humidity on in vitro FPF where the error bars represent standard deviations ($n = 2$ devices per time point/condition, four determinations per device).

the Clickhaler dry powder inhaler to deliver a pilot formulation of a novel compound. The study has shown that this drug/device combination was able to deliver a consistent delivered shot weight and a consistent emitted dose in line with current Food and Drug Administration recommendations (Food and Drug Administration, 1998) in addition to providing a high RF of drug. This indicates that significant levels of the drug can potentially be delivered consistently to the lungs. Furthermore, the study evaluated a pilot formulation and a process of optimization would be

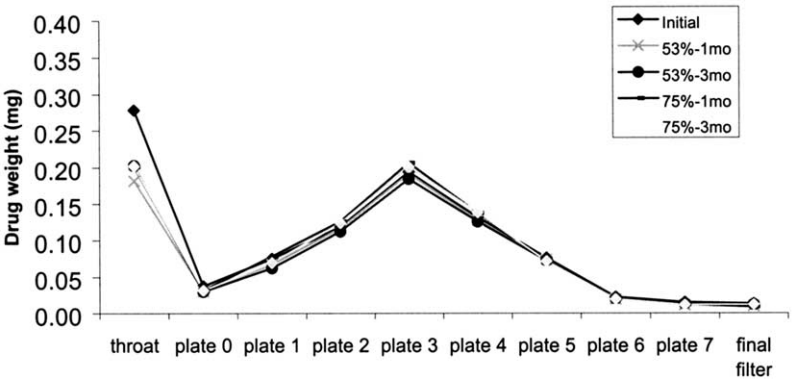

Fig. 6. The effect of storage at different relative humidity on the aerodynamic particle size distribution ($n = 2$ devices per time point/condition).

Table 3
Stability data for moisture content

	Initial	53% RH		75% RH	
		1 month	3 months	1 month	3 months
Mean (mg)	4.7	5.3	5.2	5.2	5.4
S.D.	0.12	0.12	0.10	0.08	0.00
R.S.D. (%)	2.5	2.2	1.9	1.6	0.0

anticipated to tighten performance specification. Additionally, the unprotected devices exposed to various levels of relative humidity for up to 3 months did not suffer any deterioration of key in vitro performance parameters. These results indicate the feasibility of using a novel compound in combination with the Clickhaler to deliver drug to the pulmonary region. The application of this delivery device to other drug substances is under investigation. The demands and delivery requirements of each drug substance must be considered on a case by case basis and, therefore, data from this feasibility study may not be directly applicable to other drug substances.

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