

FLEXIBLE, SMART AND LOW COST: THE MICRODOSE DPI, A TRUE PLATFORM INHALER

MicroDose Technologies is developing what could be the first electronic dry-powder inhaler to reach the market. Here, F. Scott Fleming, the company's Senior Vice-President, Sales and Marketing, explains how to retain all the advantages of electronics while keeping the cost down.

Let us begin by busting a myth. When it comes to inhaler design, incorporating electronics equates to high cost. That's the myth, but the truth is using electronics to create a "smart" inhaler does not have to result in an expensive device. MicroDose Technologies has developed a next-generation electronic dry powder inhaler (DPI) which utilises a piezo vibrator to deaggregate and aerosolise drug powders packaged in sealed blisters. This inhaler has a simple design, has a surprisingly low estimated cost to manufacture on the order of USD \$10.00, and is reusable for up to six months or longer. The MicroDose DPI, because it is re-usable, is a cost effective alternative to lower-cost, but disposable DPIs such as GSK's Diskus, which provides one month of use.

How can it be so inexpensive? The answer is simple. It is a fair assumption to say that it would be costly to develop and manufacture speciality electronic components for an inhaler from scratch. However, MicroDose has realised that it is also completely unnecessary to do so. The electronics industry manufactures a vast range of highly advanced components for the mass consumer market, and due to the high volumes and rapid development cycles, can offer them quite inexpensively. MicroDose has simply and effectively leveraged a technology transfer, and designed its inhaler around the use of these everyday components. Not only this, but it has also built a robust patent estate around its system based on the technology's specific applications in pulmonary delivery.

With the outdated ideas about electronics and expense debunked, we are now free to move on to examine the rich benefits that an electronic DPI can bring. These benefits are not of the incremental kind. Much more than merely giving a "slight edge" over alternative inhaler formats, the benefits MicroDose's electronic inhaler brings are both significant and manifold, having a posi-

tive impact on almost every aspect of the device including pharmaceutical, therapeutic, commercial and regulatory considerations.

HOW IT WORKS

Before examining what the inhaler can do, let us take a brief look at the device itself and then discuss how it works.

The MicroDose DPI is highly design flexible. Figure 1 shows just one possible iteration of the design for the purposes of identifying the main parts. The example device shown has a multi-unit dose design and incorporates a dose counter window. The MicroDose DPI can be designed to be reusable, accepting either single dose or multi-unit dose disposable cartridges.

Figure 2 demonstrates the four simple steps for using the inhaler, which are the same steps involved in using any standard DPI: open cap; advance dose; inhale; close cap. One crucial difference is that, unlike standard mechanical DPIs, patients can be directed by indicator lights and/or other feedback stimuli. The "Inhale Now" light tells the user that the device is ready to use and that they are inhaling properly. The "Dosing Done" light indicates that the dose has been correctly delivered and that the user can stop inhaling. MicroDose's inhaler is the only DPI which gives patients active feedback during administration in this way. Moreover, because the DPI is electronic, the type of feedback and the way the feedback is delivered (light or sound for example) are easily adapted.

The device uses a piezoelectric vibrator to deaggregate the drug powder packaged in either moisture-resistant aluminium or plastic blisters. The blisters are pierced with small needles prior to dosing to creating openings into the flow channel of the device. The device is breath-activated, i.e. the piezo is activated when an inhalation sensor detects a threshold level of the patient's inspirato-



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ry airflow. The flow sensor is directional, meaning that the inhaler is activated only upon inhalation, and not if the user exhales into the device.

The piezo transducer converts electrical energy to mechanical energy (vibration), which is transferred through the blister into the powder. This mechanical energy levitates and disperses the powder, and creates air pressure at the small holes in the top of the blister. These pressure pulses create high velocity jets that provide the mechanism by which the powder is both finely deaggregated and evacuated from the blister (see figure 3). Fine powder emitted from the blister is entrained in the patient's inspiratory airflow and inhaled into the lungs. Since the piezo operates at an ultrasonic frequency, vibrating tens of thousands of times a second, the powder is jetted from the blister very rapidly and in what appears to be a continuous "smoke-like" stream. The designed intent is to deliver the dose in a single inhalation.

Because the piezo vibrator generates the energy needed to deaggregate and aerosolise the powder efficiently, the need for high and forceful inspiratory flow to assure drug delivery is eliminated.

The inhaler and its related blister packaging are protected by 6 issued US patents together with multiple foreign patents and patents pending.

ELECTRONIC ADVANTAGES

Before discussing specific advantages, it is important to emphasise that MicroDose's digital format allows it to take advantage of the dramatic breakthroughs taking place in consumer electronics, where size, processing, storage, and interconnectivity are advancing at a staggering rate.

We shall stay with patient air-flow as we begin to explore the benefits and advantages – many of them unique – which the MicroDose inhaler brings. One of the Holy Grails of inhaler design is flow rate independence, and MicroDose's DPI achieves this challenging objective, with flow-rate having little to no effect on the inhaler's performance within normal inter- and intra-patient variability. Data from studies testing the delivery of a spray-dried peptide from the DPI at three different flow rates is presented in figure 4.

The MicroDose inhaler also achieves a second Holy Grail for inhalers, that of orientation independence. With the MicroDose DPI, the dose delivered remains the same whether the device is held vertical (with the mouthpiece pointing either up or down) or horizontal (with the intended "top" side of the device facing up or down), or anywhere in between (See figure 5). This is not the case with pMDIs and many of the marketed DPIs.

Because it is breath actuated, the potential performance variability introduced by varying patient co-ordination is also avoided.

The attributes described above are all exam-

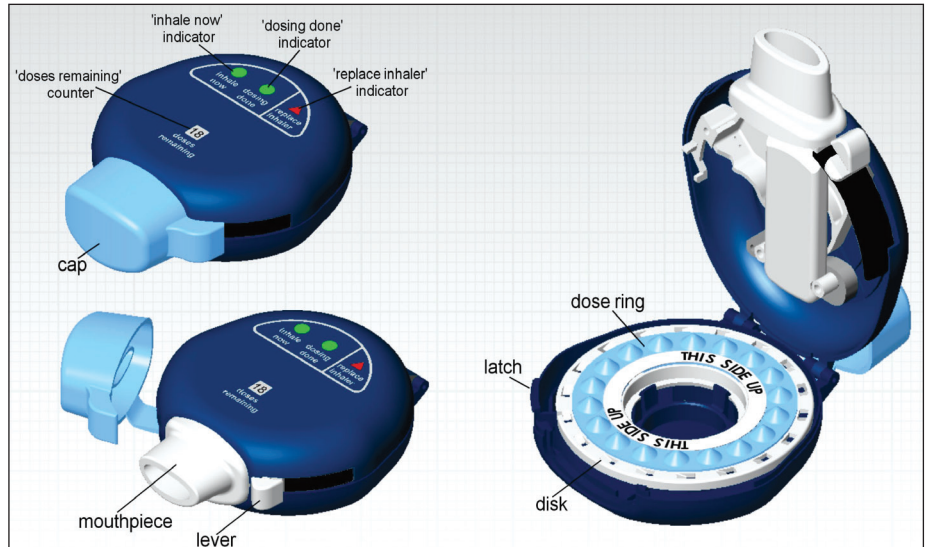


Figure 1: A view of one design iteration, to show the core components

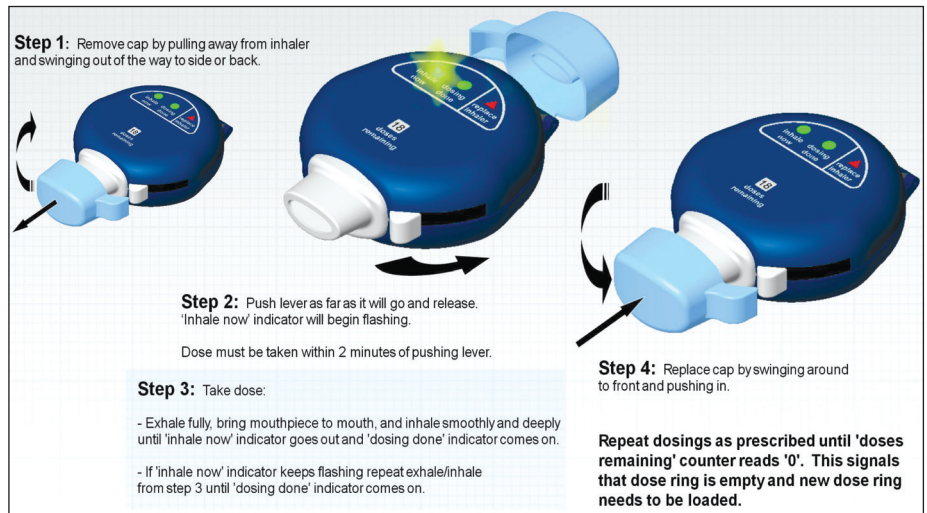


Figure 2: Intuitive, four-step procedure for use

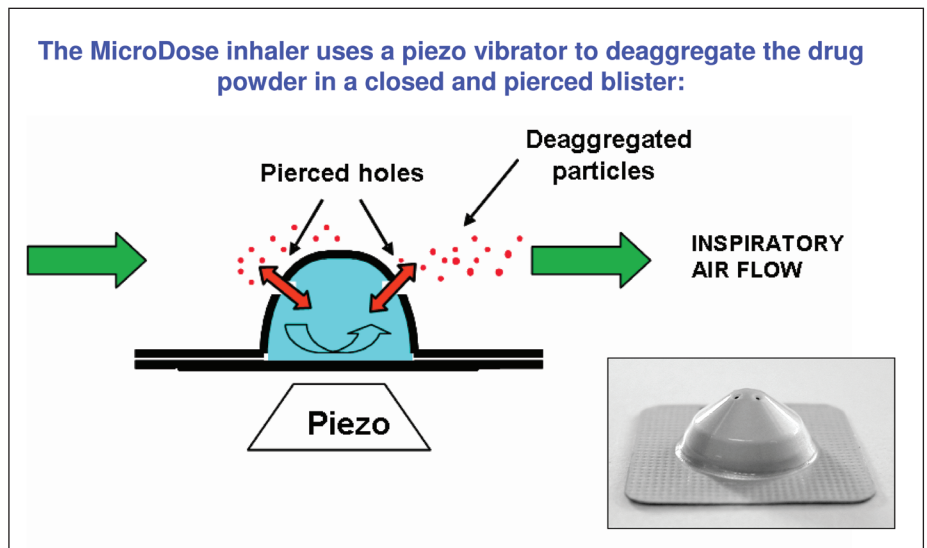


Figure 3: Principle of operation

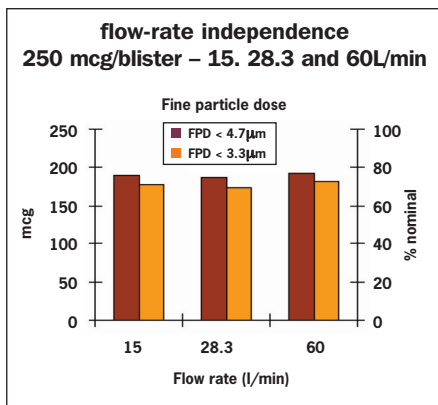


Figure 4: Graph showing constant performance, independent of variable flow rates

ples of the robustness of the MicroDose DPI's design, where the inhaler's function and performance are not compromised by the many variable factors that inhalation devices may encounter in real use. Attributes such as flow-rate and orientation independence, proper dosing feedbacks, etc. make the device easier for the patient to use correctly, whilst the efficiency of the core technology yields significant benefits in in vitro aerosol performance which should help to meet the increasingly higher performance standards established by regulatory agencies worldwide.

However, while an inhaler has to be constant and robust, it must also be flexible and readily adaptable in other ways in order to accommodate a variety of uses and users as well as the varying needs of the market.

A TRUE PLATFORM FOR PULMONARY DELIVERY

Perhaps one of the most important advantages is the fact that the MicroDose DPI is readily adaptable to different drug compounds and formulations, making it a true platform technology

applicable across a broad product pipeline. This platform capability translates to reduced risk, time and cost for those companies with multiple candidate compounds who otherwise might have to identify and develop multiple technologies in order to bring its products to market.

The majority of DPIs on the market today have been developed for a specific compound and optimised for a particular formulation. They are efficient at delivering their intended product but if the developer decides to try using it for another compound in the pipeline, complete and fundamental device re-engineering might be required. Sometimes the device must be stripped back to the extent that the journey to the new optimised configuration is so long that it is more appropriate and less complicated to start over by sourcing an entirely new device more suited to the new job.

The MicroDose DPI, in contrast, exhibits unparalleled flexibility, often requiring nothing more than simple adjustment of the piezo transducer drive circuitry in order to optimise it for delivering a new compound. Thus a company licensing-in the MicroDose inhaler can think farther and wider about applications throughout its current and future pipeline. The cost, risk, timeline and strategic advantages are clear.

The MicroDose inhaler has been tested successfully with more than 30 different compounds for both local and systemic delivery, including small molecules such as corticosteroids, long- and short-acting beta agonists and anticholinergics, as well as proteins and peptides, including insulin. The DPI is also capable of delivering formulations produced by a wide variety of processing techniques including: jet-milled pure drug, jet-milled pure drug blended with lactose; spray-dried pure drug; co-spray dried drug and excipients; super critical fluid-processed powders; and combination products.

Across most of these compounds and formulations, the DPI has maintained:

- high efficiency of emitted dose (>90%)
- high fine particle fractions (from 50 to as high as 95% as a percentage of emitted dose, less than 5.8 microns, depending on formulation type and mean particle size of the powder)
- excellent dose-to-dose reproducibility (~2-4% RSD)

DESIGN FLEXIBLE

While the ability to maintain excellent technical performance across the product pipeline is an essential foundation for a true platform technology, the inhaler must also fit with the various clinical indications for which the compounds it delivers are being developed. Crucially, it must furthermore be versatile enough to suit the different patient populations that will be using the device.

The small packaging of the micro-electronics making up the core functioning elements in the MicroDose DPI allows for tremendous design flexibility of the housing or body of the inhaler. This enables the shape of the device and (as mentioned previously) the nature of the dose feedbacks, to be readily modified to suit, for example, geriatric and paediatric populations, or specific diseases. Design features for reasons of aesthetics, product differentiation and branding can be easily added. Additional features such as security codes and lockouts to prevent overdose and/or misuse are also readily incorporated.

Importantly, while these surface modifications have a significant impact on the therapeutic and commercial success of the device, the "nuts and bolts" of the device, the pharmaceutical delivery technology within, is not disturbed. The upshot of this is that the marketing team and those responsible for designing the look and feel

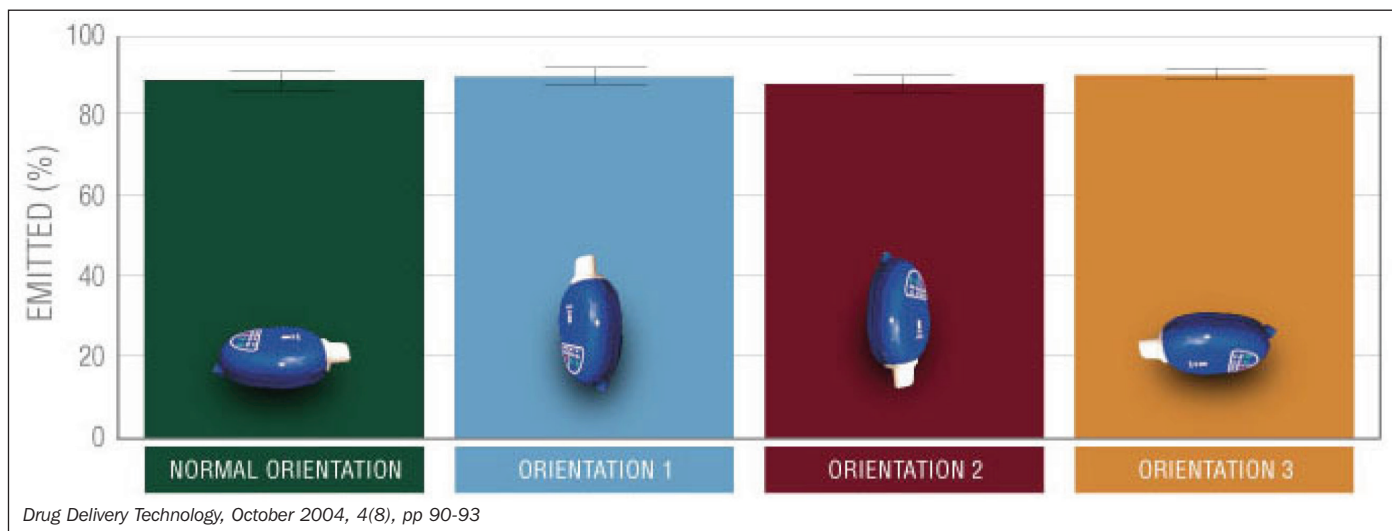


Figure 5: Graph showing constant emitted dose at various device orientations (% dose emitted ex-device, 28.3 L/minute)

and strengthening the brand need not be forced to reach a compromise with the R&D team, which is concerned with maintaining performance standards such as high emitted dose and fine particle fraction in order to ensure therapeutic efficacy.

PRODUCT DEVELOPMENT UNDERWAY

The MicroDose DPI is certainly a next-generation inhaler. However, it is by no means still at the concept phase. The most advanced product successfully completed its second Phase I clinical trial with inhaled insulin earlier this year with results to be announced shortly.

MicroDose Technologies has a two-fold business strategy. One part is to create improved partnered products by combining proprietary drug delivery technologies with pharmaceutical and biotechnology company compounds.

The other is to develop pharmaceutical products in-house using our proprietary delivery technologies with generic drug substances, for late-stage partnering, co-marketing or sale. These include respiratory compounds, products for diabetes and pain, and proteins and peptides.

MicroDose's partnered programmes include; a multi-product development and licensing

agreement with Novartis for its proprietary respiratory compounds, the development of an inhaled insulin product through QDose, its joint venture with Vectura, and also an inhaler for the systemic delivery of a nerve agent antidote for the US Department of Defense, in co-development with the University of Pittsburgh, which will enter clinical trials later this year.

Pulmonary drug delivery is not MicroDose's sole area of focus. The company also has a fixed-dose-combination oral dosage technology, PolyCap™, which allows two or more drugs to be combined in a single capsule, but separated by a physical barrier. Internal development programmes utilising the PolyCap™ technology are underway in the areas of diabetes, hypertension and hyperlipidaemia. MicroDose also has proprietary battery-operated, electromechanical needle-free system patents. MicroDose, located just North of Princeton, New Jersey, US, is privately held and has been funded by institutional and angel investors since it was founded in 1998.

SUMMARY

This article describes a highly versatile, flexible, second-generation inhaler. It is an inhaler

that makes a material contribution to ensuring the development success not just of one or two carefully picked compounds that meet the criteria to fit, but of entire broad pipelines of products for local and systemic pulmonary delivery, for which it can be readily adapted.

It is on target to reach the market within the timeframe MicroDose planned and, if successful, should be the first electronic dry-powder inhaler available. The MicroDose inhaler achieves the Holy Grails of orientation and inspiratory flow-rate independence, and it is the only DPI with active dose feedbacks to patients. It is highly efficient, and exhibits excellent dose reproducibility. It is portable, pocket-sized and discreet, and readily customisable for a varying range of patient populations. It is a cost-competitive, re-usable device.

MicroDose Technologies is a financially independent and well established drug delivery leader with three platform technologies protected by a broad and robust global patent estate. It has a proven track record as a winning partner with leading pharmaceutical, biotechnology and drug delivery companies, academic institutions and government bodies. MicroDose is keen to develop new relationships with industry.