

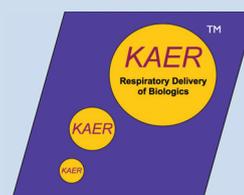
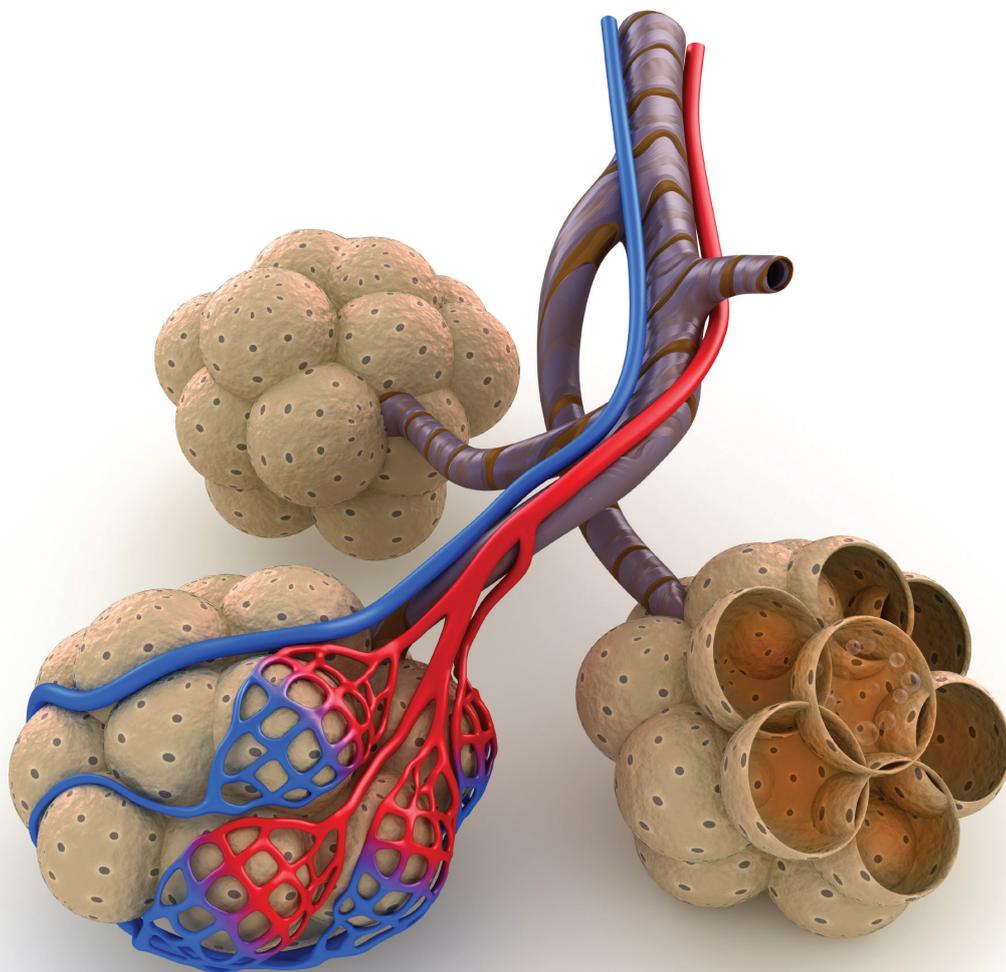
PULMONARY & NASAL DRUG DELIVERY: COULD INHALABLE DELIVERY BE APPROPRIATE FOR YOUR SMALL MOLECULE OR BIOTHERAPEUTIC?



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Pulmonary & Nasal Drug Delivery: Could Inhalable Delivery Be Appropriate for Your Small Molecule or Biotherapeutic?

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Frederick Furness Publishing

48, Albany Villas, Hove, East Sussex, BN3 2RW
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BRINGING THE PATIENT'S VOICE TO NASAL DRUG DELIVERY

Nasal MDI's were phased out in favour of aqueous sprays when CFC propellants were banned. However, here, Louise Righton, Global Market Development Manager, 3M Drug Delivery Systems, describes how patient preferences and numerous advantages over aqueous pump sprays combine to make 3M's new Nasal MDI device (with HFA propellant) an attractive alternative.

The market for topical nasal sprays for allergic rhinitis is in excess of 200 million units per annum, and the leading brands achieve approximately \$1 billion retail sales.¹ It is estimated that 400 million people suffer from allergic rhinitis worldwide, making the patient population the largest of the preventable chronic respiratory diseases.² Whilst rhinitis is not life threatening, it significantly affects quality of life for sufferers.

The mainstay of treatment is aqueous pump sprays, particularly for those patients who prefer to treat topically because of the higher perceived efficacy of locally acting medication, and the desire to avoid the systemic side effects of oral dosage forms.³

Drugs formulated into aqueous sprays include the corticosteroids, such as beclometh-

asone dipropionate, fluticasone propionate, mometasone furoate, and the more recently introduced ciclesonide. In addition, antihistamines such as azelastine and mast cell stabilisers such as cromolyn sodium are presented in this format. Several companies are developing combination antihistamine and corticosteroid products in the familiar aqueous spray format.⁴

However, patient research has shown that the use of aqueous sprays is typically an unpleasant experience for the user, with drug formulation dripping down the back of the throat, which can cause a bad aftertaste or even irritation, or running back down the nose, which can reduce the dose retained in the nasal cavity and cause discomfort and embarrassment.⁵ For this reason, patients tend not to use their sprays when outside of the privacy of their own home – a drawback when the triggers

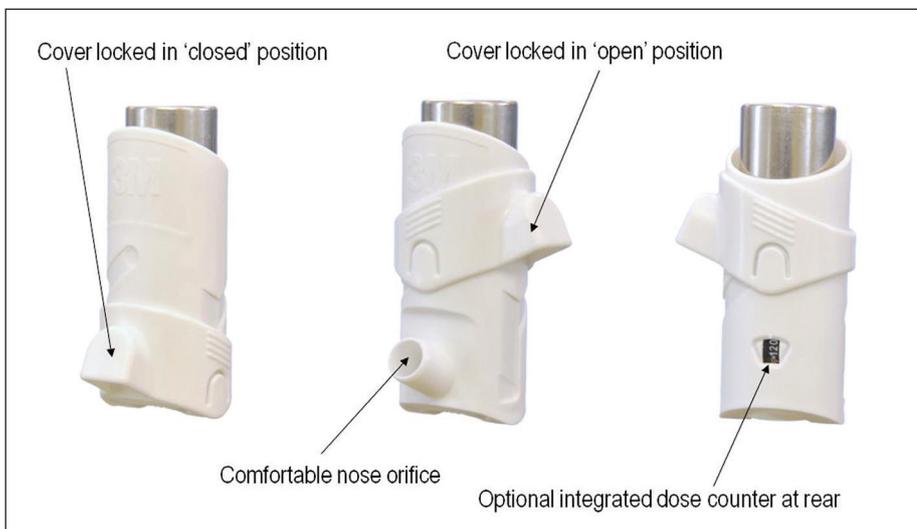


Figure 1: The 3M Nasal MDI from 3M Drug Delivery Systems.



Mrs Louise Righton
Global Market Development
Manager, 3M Drug Delivery
Systems
T: +44 1509 613626
F: +44 1509 613099
E: lrighton@mmm.com

3M Health Care Limited
3M House, Morley Street
Loughborough
Leicestershire
LE11 1EP
United Kingdom

www.3m.com/dds

for allergic rhinitis include pollen and pollution, which affect the patient outdoors.

As pharmaceutical companies develop more advanced treatments for this therapy area, or look towards lifecycle management of existing branded treatments to protect against generic entrants, patient preferences *must* be taken into account. The patient is increasingly influential in determining which products will be prescribed, and in some countries these products are available over the counter. In recent years sufferers have had no choice but to use aqueous sprays for topical application, but new research reveals that patients want an alternative.⁵

AN ALTERNATIVE TO THE AQUEOUS PUMP SPRAY

Nasal metered dose inhalers (MDIs) were commonly used to treat allergic rhinitis until the phase-out of chlorofluorocarbon (CFC) propellants in favour of the “ozone-friendly” hydrofluoroalkane (HFA) propellants following the signing of the Montreal Protocol.⁶ Nasal MDIs were not included alongside pulmonary MDIs in the “essential use” exemption. Leading nasal MDI products included Rhinocort (from AstraZeneca UK Ltd), developed and manufactured by 3M Drug Delivery Systems in partnership with AstraZeneca, as well as Nasacort (from sanofi-aventis, France), and others.

Given the complexity of reformulation using HFA propellants for the first time, developers opted to reformulate instead into simple aqueous systems. However, anecdotal evidence from patients suggests that many believed aerosols to be more effective than the aqueous sprays that replaced them, and they lamented their demise, hoping for a return to the market of key aerosol brands.⁷

The unpleasant experiences associated with aqueous sprays can be overcome using MDI devices, whereby medication is delivered in the form of a quickly evaporating “no-drip” spray. In addition, new technologies such as ergonomic designs and dose counters can be incorporated to add further differentiation and command a price premium.

3M has developed one such nasal MDI device and this is shown in Figure 1. MDI devices can add differentiation using human design factors in contrast to the purely functional and relatively generic designs of most aqueous pump sprays. A range of currently marketed aqueous pump sprays is shown in Figure 2.

When considering MDIs for nasal use, one question that can arise is whether an MDI is at risk of causing irritation of the nasal cavity, due to the velocity of the plume and also the use of ethanol in some formulations. In fact,



Figure 2: A range of currently marketed aqueous pump sprays.*

nasal MDIs have been demonstrated to be safe and well tolerated in a range of clinical trials, including studies performed on an HFA formulation of triamcinolone acetonide (Nasacort HFA, sanofi-aventis)⁸ and an HFA formulation of ciclesonide (Omnaris HFA, Sunovion).⁹ Of course, the historical success of nasal MDIs also inspires confidence, particularly when one considers that the newer HFA propellants give a “warm” plume in comparison with the “cold Freon effect” of the old CFC propellants.

A second question is the risk of unintended deposition in the lung due to the high velocity delivery of small particles. In fact, it has been demonstrated that no significant deposition

occurs in the lung when a nasal MDI is administered¹⁰ and this finding is supported by recent studies demonstrating the safety of several corticosteroid nasal MDIs.^{8,9,11}

There is evidence that MDIs may be more effective than aqueous pump sprays. The successful nasal retention of drug delivered via an MDI has been demonstrated as shown in Figure 3, which illustrates that only 18% and 15.4% of the dose for the one-position and two-position studies, respectively, had been cleared after 30 minutes, with 64.5% and 65.3% of the respective doses remaining *in situ*.¹⁰

This contrasts with the almost total clearance of droplets delivered by an aqueous pump

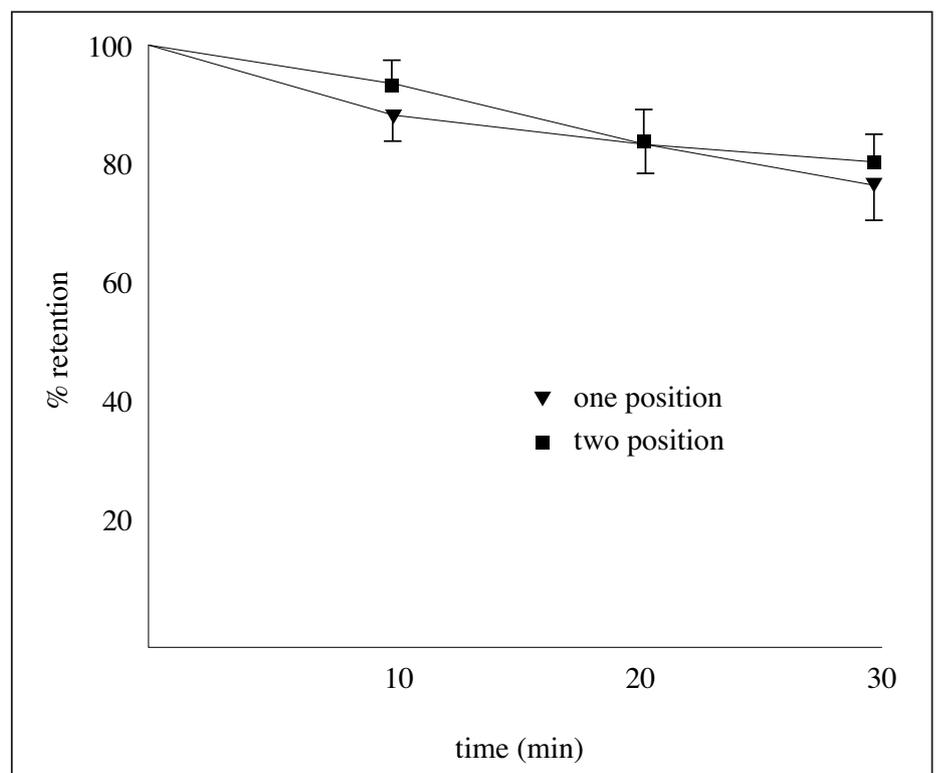


Figure 3: Mean (\pm SEM) Retention of Aerosol at the Initial Site of Deposition in the Nose, Expressed as a Percentage of the Amount Initially Deposited, for One-Position and Two-Position Studies. (Reproduced with permission from “The Nasal Distribution of Metered Dose Inhalers”, Newman, SP et al, *J Laryngol Otol*, 1987 Feb; 101(2):127-32).

“PATIENTS LIKED THE IDEA OF THE NEW 3M NASAL MDI DEVICE, WHICH THEY PERCEIVED AS OVERCOMING MOST OF THE PROBLEMS ASSOCIATED WITH AQUEOUS PUMP SPRAY PRODUCTS.”

spray in an average of 30 minutes.¹² The high velocity of an MDI spray deposits drug primarily in the anterior region of the nasal cavity where there are fewer nasal cilia available for clearance, and the small particles delivered by an MDI are less partial to clearance versus the large droplets from an aqueous pump spray.³ This superior retention also means that MDIs are more suited to patients with runny noses.³

More recently, studies have evaluated the risk of sub-therapeutic dosing with the “force-dependent” aqueous pump spray format, which has been shown to deliver large variances in delivered dose with different patient groups,¹³ a drawback that is not seen with the MDI format, long recognised for its excellent dose consistency.¹⁴

DEVELOPMENTS IN THE TOPICAL ALLERGIC RHINITIS MARKET

As nasal corticosteroids go off-patent and generics enter the market, pharmaceutical companies are reformulating their products to add additional indications or to improve patient benefits, for example once-a-day dosing, and patient-friendly devices. One such recent product introduction is Veramyst (GlaxoSmithKline, UK), which utilises a “side-actuated” device incorporating a viewing window to enable the patient to determine how much medication is left in the bottle.

An alternative to this basic viewing window is a dose counter – a technology which can be incorporated into a nasal MDI and which is already widely used in the respiratory category. 3M’s Nasal MDI device is available with an integrated dose counter based on 3M technology which has been FDA-approved in conjunction with an MDI product.

3M’s research with patients shows that the introduction of a dose counter gives them a feeling of security, enabling them more accurately to monitor doses remaining in their device and to renew prescriptions without the inconvenience of running out of medication.^{5,15}

PATIENT ASSESSMENTS OF AQUEOUS PUMP SPRAY DEVICES

3M Drug Delivery Systems conducted qualitative research with 64 sufferers of seasonal and/or perennial allergic rhinitis, half of the sample in the US and half in the UK.⁵ The

commonly available aqueous pump sprays were deemed a necessary evil rather than a fully accepted form of treatment.

In preparation for using an aqueous spray, users describe a feeling of having to “steel themselves” for the shock of the administration, and they have to have tissues handy in order to deal with the embarrassing nasal run-off post-administration. During use, they describe shock as the product “hits”; an unpleasant sensation in the sinuses; an unpleasant taste sometimes accompanied by irritation in the throat due to post-nasal drip; and finally the need for privacy to deal with the aftermath. Post-administration, the patient attempts to retain the product in the nostrils by holding the breath, trying not to swallow or blow the nose.

Patients questioned the efficacy of aqueous sprays as a result of the nasal run-off. The functionality of aqueous spray devices was also queried – particularly the force-dependent nature of actuation, which means that an inaccurate dose can be administered.

During development of the 3M Nasal MDI some of the industry’s cutting-edge processes and technologies were used to produce moulded samples to facilitate pharmaceutical data generation, and allow patient focus groups to interact with the device. Some of the technologies used included rapid prototyping, rapid tool manufacture and chromatic evaluations (colour-coded deviation display). These processes have allowed 3M to provide moulded samples from the initial generation of CAD in weeks instead of months. Patients liked the idea of the new 3M Nasal MDI device, which they perceived as overcoming most of the problems associated with aqueous pump spray products.

The main perceived benefit of the 3M Nasal MDI was the “dryness” of the spray and the elimination of the unpleasant sensations and taste associated with the “wet” aqueous sprays. This meant that users would no longer feel embarrassed to use their spray in public, and would be more likely to carry it around and use it when needed. In addition, the styling of the device was appreciated, being described as compact and portable, and the “twist-and-lock” cover was particularly appealing as an aid to hygiene. Finally, the device was perceived to be more effective than an aqueous pump spray device due to

the metered dose mechanism, which patients understood meant a consistent and correct dose with every administration.

ADDITIONAL CONSIDERATIONS FOR DEVELOPERS

In addition to the voice of the patient, there are other considerations for the pharmaceutical company considering the development of a topical allergic rhinitis product.

The MDI device is a low-risk choice, given that it is familiar to regulators, physicians and patients alike due to its more than 50 years track record in pulmonary drug delivery,¹⁴ and previous use in the nasal drug delivery marketplace. Further, business considerations such as the ability to create a fast line extension of a successful inhaled corticosteroid in the respiratory market make the MDI an attractive proposition.¹⁶

Unit cost of product is always a consideration, and the low cost of MDIs, particularly on a cost-per-dose basis, means they will remain an attractive delivery system.¹⁶

MOVING TOWARDS PATIENT-FOCUSED DEVICES

The patient’s voice has become increasingly important in pharmaceutical device development, and developers acknowledge that the patient’s interface with the device is crucial to its success.¹⁷ Evolution in device design will be driven by more informed consumers, confident to demand products to meet their needs and fit their lifestyles. Allergic rhinitis patients demand attributes for topical products that are currently not met by aqueous pump sprays.⁵

In the current economic climate, a convincing business case must be made for device developments. Drug delivery innovators such as 3M believe that pharmaceutical products should not be any less consumer-researched and design-optimised than other consumer products, and that a “device-edge” is possible and worthwhile in the attractive allergic rhinitis market.

CONCLUSION

Nasal MDIs were the leading delivery systems for topical allergic rhinitis medications until the CFC phaseout. In recent years, allergy sufferers requiring topical application have had no choice but to use aqueous pump sprays to treat their rhinitis. Research amongst patients demonstrates that they want an alternative.

Whilst there will undoubtedly be a place in the worldwide marketplace for low-cost aqueous spray devices for generic applications, it is

clear that the voice of the patient will increasingly be heard in nasal device development.

Patient and physician choice is set to expand further as improvements in the aqueous spray format are brought to market and, in addition, differentiated MDI devices are welcomed into this market once more.

*Boots Hayfever Relief Nasal Spray is a trademark of Boots Company plc; Nasacort® Allergy Nasal Spray is a registered trademark of sanofi-aventis; Flixonase Allergy™ Nasal Spray is a registered trademark of GlaxoSmithKline; Nasonex® is a trademark of Merck & Co; Beconase® Hayfever relief for Adults is a registered trademark of GlaxoSmithKline; and Rinholast® Nasal Spray is a registered trademark of Meda Pharmaceuticals Ltd.

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HDA - A NEW PULMONARY DRUG DELIVERY PLATFORM CAN PROVIDE FOR MORE EFFICIENT AND SAFER DELIVERY

In this article, Peter Boonen, Managing Director, Stirling Products Limited, introduces the High Density Aerosol (HDA) Delivery Platform, a fully patented pocket nebuliser with a new ultrasonic aerosol-generating device. He describes the system's advantages over dry-powder devices and conventional nebulisers, clinical trial results in the delivery of respiratory and non-respiratory drugs, and improved safety compared with oral administration.

Despite a general acceptance within the industry of the superiority of pulmonary drug delivery, the delivery of drugs via the lung is currently still massively under-exploited – both for respiratory diseases and for systemic delivery.

This is largely because of the delivery issues associated with the **current delivery systems that are predominantly dry-powder based**. Pfizer's Exubera was promised to herald in the next-generation dry-powder delivery technology – more than US\$1 billion was reportedly written off when this project was abandoned.

Although hundreds of millions of dollars have been and continue to be spent on dry-powder delivery applications, the versatile and effective multi-drug pulmonary delivery device has to date eluded development. One of the reasons that this is believed to be the case is that there has been such a great focus on dry-powder systems. This is despite the knowledge that the lung is naturally designed to deal with moisture or liquid (humidity), and not powder (dust) which its natural inbuilt defences are structured to reject.

A new development being commercialised by Australian based Stirling Products Limited is positioned as a potential industry breakthrough. This small life sciences company is in the process of commercialising a delivery platform that overcomes the major problems of pulmonary drug delivery.

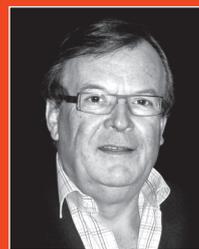
HDA DRUG DELIVERY - A MAJOR BREAKTHROUGH

The High Density Aerosol (HDA) platform technology (see Figure 1) introduces a new class of aerosol-generation device that is suited for use in a wide range of applications. It offers a highly effective method of delivering a diverse range of traditional pharmaceutical and biotechnology agents including both respiratory and non-respiratory drugs.

This HDA technology has proven it is highly efficient in delivering respiratory drugs such as albuterol sulphate.¹ Additionally, where other technologies have failed, research also shows this new HDA technology is effective in delivering drugs such as insulin and pain relief medication via the respiratory route.

A recent clinical study published in the Journal of Sexual Medicine demonstrated that HDA technology was highly effective in delivering vardenafil hydrochloride.² Using just a fraction of the normal tablet dose, the HDA technology reached the same plasma concentrations much faster and with less variability.

This HDA technology offers major opportunities for drug development and can effectively provide for the equivalent of the extension of patent life for existing agents merely by uniquely being able to provide for similar benefit with far lower-dose formulations.



Mr Peter Boonen
Managing Director

T: +61 2 9299 9270
E: peter.boonen@stirlingproducts.net

Stirling Products Limited
Level 1 - 275 George Street
Sydney
NSW 2000
Australia

www.stirlingproducts.net

ADVANTAGES OF HDA TECHNOLOGY

The HDA Nebuliser **delivers at least three times the aerosol** concentration of conventional ultrasonic devices (see Figure 2) and, unlike dry-powder inhalers, the HDA Nebuliser delivers the drug to the deep lung in a dissolved state with much faster absorption and much lower transportation losses. This technology represents a new class of drug delivery device offering multiple advantages over existing technologies.

These advantages include:

- **can be used for multiple drug products**
- **constant aerosol concentration** during inhalation – matched to natural inhalation
- **eliminating the need for a fan** to transport aerosol to the user
- **minimal residual level** of the liquid to be nebulised
- **negligible transportation losses** of the drug on the pathway to the lungs
- **true breath-activation**
- suitable for all **ages** of patients, especially children and the chronically ill
- **no moving parts** - increases reliability and battery life, reduces production and maintenance costs and improves convenience in service
- **low power consumption**
- **noiseless**
- **pocket size device**
- **disposable drug capsule** - key locked
- **easy to operate**
- **rapid delivery** of drug where needed (e.g. pain relief)

These advantages and features provide for true portability and greater effectiveness through reduced weight, size, cost, power consumption, reduced velocity and patient discomfort and reduced aerosol (drug) loss during transportation. Patients can inhale normally without gagging or special training.

NATURAL DELIVERY

Drugs, or any other material, administered to the lungs are naturally subjected to active metabolic barriers throughout the delivery process. As Stirling's HDA Delivery administration is in **atomised liquid formulation**, matched to natural breathing, the delivered drug largely avoids or minimises the effect of three of the major problems generally associated with pulmonary delivery of drugs – all being part of the body's natural defence mechanisms (especially to dust or powder).

- i) The mucosal escalation activated through the recognition of a foreign substance (drug), results in the drug-laden saliva



Figure 1: The HDA device

- ii) Coughing – a natural defence to the sensing of foreign substance (drug) introduction. A common problem of dry-powder administration resulting in patient's coughing up the drug, which was intended for pulmonary delivery, and swallowing it.
- iii) Within the lungs, macrophages, lymphocytes, neutrophils and mast cells can release proteases and peptidases when stimulated by introduction of any foreign substance (drug). The Stirling HDA Platform drug administered product being in the sub-5 micron range ensures that firstly, far more active product is delivered to the deep lung; and secondly, enzymatic degradation of the administered drug is thereby minimised.

In meeting the industry needs for pulmonary drug delivery HDA technology opens up new frontiers for treatment of many diseases in diverse modalities such as respiratory disorders, mass vaccination, obesity, HIV, neurology,

pain relief, diabetes, oncology, osteoporosis, migraine, growth hormones anaesthesiology, sexual dysfunction, ophthalmology, ENT, nuclear medicine and wound management.

This technology is able to effectively deliver agents such as insulin, hormones, proteins, interferon, antibiotics, heparin and radio aerosols.

RESEARCH DATA

To date all testing and trials of the Stirling HDA Drug Delivery Platform technology have shown it to provide for a superior and far more versatile delivery device than other pulmonary delivery devices. In general terms the HDA Drug Delivery Platform, using encapsulated single-dose liquid drug product, can more efficiently deliver the aerosol drug product than any dry-powder dispensing device. It can produce this nebulised aerosol at much higher flow rates than any current portable nebulisers, thus reducing the time taken to administer the dose.

The technology that enables this within small portable nebulisers is fully patented.

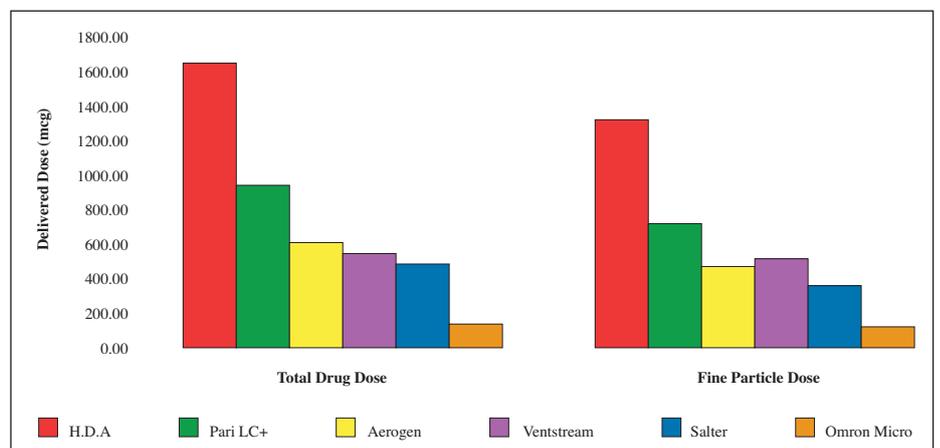


Figure 2: Comparison of delivered dose results from HDA device versus other nebulisers in the delivery of albuterol.

Most importantly, HDA nebulised drug delivered to the lung will provide for far improved safety in drug administration, as far less active drug (approximately 10-15%) is required to provide the same benefit as an orally administered drug, i.e. less drug – less side effects.

Trials of HDA-delivered respiratory drugs have demonstrated it to be highly effective for the administration of the following inhalation solutions used in the study: ¹

- i) Albuterol sulphate 2.5 mg / 3 ml
- ii) Cromolyn sodium 20 mg / 2 ml
- iii) Ipratropium bromide 0.5 mg / 2.5 ml

Additionally comparisons of HDA Technology *versus* standard nebulisers showed superior performance (see Figure 2).

In a clinical trial using an HDA-administered low dose of the erectile dysfunction drug vardenafil, the authors found, "... that vardenafil HCl may be administered using the ultrasonic nebuliser to reach blood levels comparable with those produced by a vardenafil 10 mg oral tablet, faster and using less drug. The two treatments are not bioequivalent, with vardenafil absorbed and eliminated faster and with less variability using the nebuliser for drug delivery. Administration via the inhalational route was

not associated with any clinically significant changes in blood pressure or heart rate, and no serious adverse events were recorded, demonstrating an acceptable safety profile". ²

HDA OPERATIONAL SUMMARY

The HDA technology uses focused ultrasonic energy to form a fountain of liquid to be nebulised that produces an aerosol from the walls of the jet that self-propels at several meters per second up a chimney-like intake tube. Atomisation of the liquid occurs at the base of the jet inside the intake tube. The micro-particle aerosol is then transported to the user by positive dynamic pressure derived intrinsically from the kinetic energy of the jet.

The HDA technology therefore does not require any compressed gas or fan driven air-flow to transport aerosol to the user. This significantly increases the aerosol concentration by both eliminating the gas/fan dilution effect and reducing the drug loss associated with aerosol condensation inside the nebulisation chamber.

COMMERCIAL OPPORTUNITY

The patented HDA technology offers a significant opportunity to target a multi-billion

market as it can be leveraged to improve drug safety profiles and thereby permit the equivalent of new patents to the improved performance versions (subject to trial validation) of some of the world's major drugs as they come off patent.

The fully patented HDA Technology offers companies within these fields major strategic advantages over existing competition and presents a number of highly lucrative opportunities for new drug molecules or patent extension programs.

Stirling Products Limited will be trialing its final pre-production prototypes in late 2011 and early 2012 and is interested in discussing exclusive HDA licensing opportunities with potential partners.

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www.stirlingproducts.net

or contact:

Peter Boonen

Managing Director

Stirling Products Limited

Ph: +61 2 9299 9270

E: peter.boonen@stirlingproducts.net

Or:

Neil Covey

Ph: +61 2 9299 9270

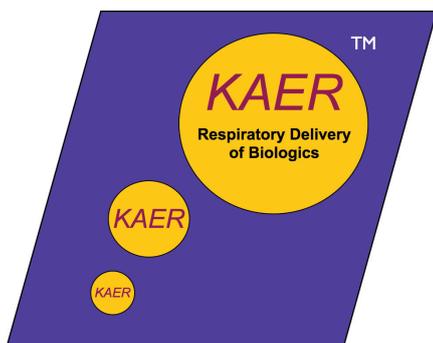
M: +61 421 346 844

E: neil.covey@stirlingproducts.net

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SUPRAER™: A NEW CLASS OF AEROSOL DELIVERY SYSTEM FOR BIOTHERAPEUTICS

The delivery of aerosols of large labile molecules to the deep lung presents formidable barriers. Herein Donovan Yeates, PhD, Chief Executive Officer of KAER Biotherapeutics, describes a new class of aerosol delivery system which directly addresses these issues. KAER Biotherapeutics™ provides respiratory aerosol delivery services and partners with pharma to deliver their biologic and large labile molecules.

Biotherapeutics comprise 30-50% of the active pharmaceutical ingredients (APIs) currently under development. There are 200 biopharmaceuticals in the market¹ with over US\$100 billion in annual sales.² For cancer alone there are some 1,185 biologicals under development.¹ Orally administered biologics are subject to digestion. Intravenous administration is not well accepted and can lead to complications.

For the treatment of respiratory diseases, aerosol administration requires a much lower dose than that administered orally or intravenously and minimises unwarranted side effects. Aerosol delivery via the respiratory tract is the preferred mode of administration for many biotherapeutics including: proteins, surfactants, oligonucleotides, antibodies, vaccines and liposomes. Described here, is a new class of aerosol delivery system suitable for the delivery of large labile molecules, including biotherapeutics.

Whereas there is a good choice of nebulisers to deliver micrograms of small molecules, the need for an aerosol inhalation system which can efficiently and rapidly deliver 10-100 mg of a biotherapeutic to the deep lung in a short time has limited the use of inhaled aerosols in the treatment of both respiratory and systemic diseases. This has become an acute issue for the delivery of biologics and other large labile molecules. For instance, aerosol administration of alpha-1 antitrypsin was proposed in 1989³ yet some 22 years later is still not an approved method of treatment of hereditary emphysema.

The delivery of tens of milligrams of biotherapeutics presents formidable barriers and practical issues for present liquid or dry powder aerosol delivery systems. These are summarised in Figure 1.

SUPRAER™ is a new aerosol delivery platform technology which overcomes all of

Liquid nebulizers	Inability to nebulize large macromolecules or high protein concentrations	Low or no output Long treatment times
	Shear-induced molecular degradation	Questionable dosimetry
Dry powder inhalers	Difficult formulation	Increased development \$
	Unwanted excipients	Increased safety pharmacology \$ Increased side effects
	High oral deposition, low variable lung deposition	Variable dosimetry Decreased efficacy

Figure 1: Limitations of present commercial nebulisers related to the delivery of large labile molecules.



Dr Donovan B Yeates
Chief Executive Officer
T: 760 480 9400
F: 760 480 9401
E: dyeates@kaerbio.com

KAER Biotherapeutics
926 Andreasen Drive, Suite 105
Escondido
CA 92029
United States

www.kaerbio.com

	Jet Type Liquid	Vibrating Mesh Liquid	Dry Powder	SUPRAER Liquid to Dry
Output	+	++	+++	+++++
Breathing Pattern	+++++	+++++	+	+++++
Aerosol on Inhalation only	+++++		+++++	+++++
Viscous & high MW	++	+		+++++

Figure 2: Characteristics of jet, vibrating mesh and dry-power inhalers related to their potential for efficient delivery of biotherapeutics to the deep lung.

these issues. SUPRAER generates a large aqueous aerosol of the active agent which is rapidly dried, concentrated and delivered on demand as a solid respirable aerosol of “pure” agent.

The characteristics of jet type, vibrating mesh and dry power inhalers related to their potential for delivering large molecules and viscous solutions are summarized in Figure 2 and compared with those projected for SUPRAER. In this table, the nebulisers have been roughly evaluated on (a) their potential to deliver masses of drug, (b) whether they can be readily adapted for an optimal breathing pattern for deep lung delivery, (c) whether the aerosol can be generated during inhalation only, as well as (d) their ability to generate respirable aerosols from high concentrations of large molecules, i.e. viscous solutions.

SUPRAER scores highly in all categories. As SUPRAER, generates large liquid aerosols and delivers them as concentrated dry-powder respirable aerosols, its potential to produce high mass output with minimal shear degradation is clear. Also, as SUPRAER initially generates large aerosols it has the potential to aerosolise more viscous solutions than typical jet and vibrating mesh nebulizers which generally target a 3 µm-diameter liquid aerosol for deep-lung deposition.

FUNCTIONAL DESCRIPTION OF SUPRAER

The major components of SUPRAER can be seen in the photo in Figure 1. The fluid to be aerosolised is fed into the nozzle holder and thus to the nozzle. This nozzle holder is inserted coaxially into a flow conditioner.

The flow conditioner has several functions. The flow conditioner conditions the high velocity dilution input air so that the aerosol has a relatively uniform air velocity across the area of the output of the attached evaporation chamber. It also partitions the compressed air between the nozzle and a counter flow tube.

The evaporation and aerosol aging chamber comprises a quartz tube where the liquid droplets are evaporated resulting in a residual dry respirable powder aerosol. The aerosol plume from the nozzle is arrested about 2.5cm from

the nozzle by a counter-flow jet of air aligned coaxial with the nozzle. The counter-flow tube is seated in the flow conditioner to ensure precise and reproducible coaxial alignment with the aerosol jet. Evaporation of the aerosol is augmented by warming the dilution air the nozzle air and the counter-flow air.

In addition, the evaporation is augmented by infrared radiation which is cylindrically focused into the chamber and reflected by a cylindrical aluminum reflector on the opposite side of the chamber. The rapidly responding infrared heater



Figure 3: Preclinical version of SUPRAER with the requisite controls to enable the optimisation of the airflows and heating parameters for each API.

is designed to have its major emission within the infrared absorption band for water. The resultant dry aerosol at the output of the evaporation tube enters a virtual impactor with radial slits. The profiles of these input acceleration slit nozzles and output slit nozzles have been designed both to reduce the pressure required for efficient operation of the concentrator and, as far as possible, to maintain a uniform flow across the area of the virtual impactor.

Most of the air is exhausted between the slits of the input and output nozzles. This air enters a concentric plenum and is filtered to prevent the release of any active ingredients into the atmosphere. There is also a space immediately distal to the concentrator which allows relaxation of the aerosol jets from the output slits. The aerosol is collected within a parabolically profiled collection cone. The output flow rate is controlled by the device connected to the output of the collection cone.

A preclinical version of SUPRAER has been manufactured to meet the needs of those who

need to deliver large masses of their active agent for evaluation of pharmacology, pharmacokinetics’ safety pharmacology and toxicology in small animals.

SUPRAER facilitates the rapid delivery of pure agent without the confounding factors related to the presence of any excipients. As the rate of drying due to radiant infrared fluxes and conduction from the suspending air can be controlled, SUPRAER’s parameters can be tailored to suit the specific molecules at hand. There is also the potential for delivering small molecules in a controlled-release matrix.

This preclinical version of SUPRAER has the requisite controls to enable the optimisation of the airflows and heating parameters for each API (see Figure 1). The controls enable selection of the nozzle pressure and concurrently the velocity of the counter-flow air. The temperatures of these airstreams are regulated with a PID controller. The dilution air flow and temperature similarly can be set to the desired value. Flow switches turn the heaters off if the flow through any heater falls below a threshold value. The intensity of the infrared radiation is continuously adjustable.

To minimise any shear-induced degradation, SUPRAER has been designed to operate with either of two very low-shear nozzles. One nozzle incorporates the flow focusing technology of Ganau-Calvo. In this nozzle, the compressed air envelops the fluid jet as it passes through the nozzle orifice. The other nozzle is proprietary to KAER Biotherapeutics in which a central air jet aerosolises a thin film of fluid at the circumference of an orifice positioned at the internal base of a cone.

PERFORMANCE

A solution of 16% bovine serum albumin was fed to the nozzle using an infusion pump and aerosolised at 1 ml/minute. The nozzle pressure was 20-24 psi and the dilution gas flow 200 litres/minute. The resultant dry aerosol downstream from the concentrator was measured for two minutes at 40 litres/minute. The mass collected was determined gravimetrically.

Typically 180-210 mg was collected. Thus, the output of the device is about 100 mg per minute.

The overall efficiency of the throughput of the device was found to be 64%. The efficiency of the concentrator alone was found to be 85%.

Red food dye number 4 (0.2%) was added as a tracer to the 16% albumin solution. Under similar conditions an albumin aerosol was sampled at 30 litres/minute by a Marple Miller cascade impactor. Each stage of the impactor was washed three times with water and the relative mass on each stage was determined spectrophotometrically at 508 nm. The cumulative mass was plotted on log-probability paper. The mass median diameter was found to be 3.4 μm . Of the collected aerosol, 85% was found to be in the respirable range, i.e. the sum of all stages up to and including 5 μm .

To determine if the aerosolised protein was degraded by passing through the nebuliser, porcine trypsin was aerosolised and collected. A solution of this trypsin was placed on a confluent cell culture. The cells were seen to detach from the substrate. No difference could be seen between the results of a similar concentration of trypsin which had not been aerosolised.

To evaluate the shape and surface characteristics of the albumin particles produced, particles at the output were collected on a 12 mm diameter Millipore filter. The filter was placed at the center

of a larger filter with similar flow characteristics. This filter was then mounted on an electron microscope stud and stored upright in a desiccator. Each sample was sputtered with palladium-gold and random images recorded on a SEM at magnification of 1500. The albumin particles were found to be spherical with a smooth surface.

APPLICATIONS

Delivery of large labile molecules

Whereas many nebulisers are pocket sized, SUPRAER has not yet been reduced to those dimensions. Thus, its competitive advantage lies in the delivery of large molecules for chronic conditions in the clinic or at home rather than as a "rescue" inhaler. Thus, suitable candidates for SUPRAER include alpha-1 antitrypsin, monoclonal antibodies, surfactant, plasmids and oligonucleotides. The preclinical version of SUPRAER enables optimisation of the important aerosol-generation and processing parameters to enable optimisation of the technology into a compact aerosol delivery system tailored for clinical use.

Animal pharmacology and toxicology

SUPRAER provides a concentrated aerosol suitable for inhalation studies in small animals. This overcomes many of the difficulties of

providing an efficient means of generating and delivering respirable aerosols for pharmacological and toxicological studies. SUPRAER has been designed to work in conjunction with KAER's small animal exposure and inhalation system, SARES™. SARES is a nose-only zero dead-space exposure system capable of delivering respirable aerosols to 12 awake rats or guinea pigs simultaneously while monitoring respiratory parameters and ECG.

ACKNOWLEDGEMENTS:

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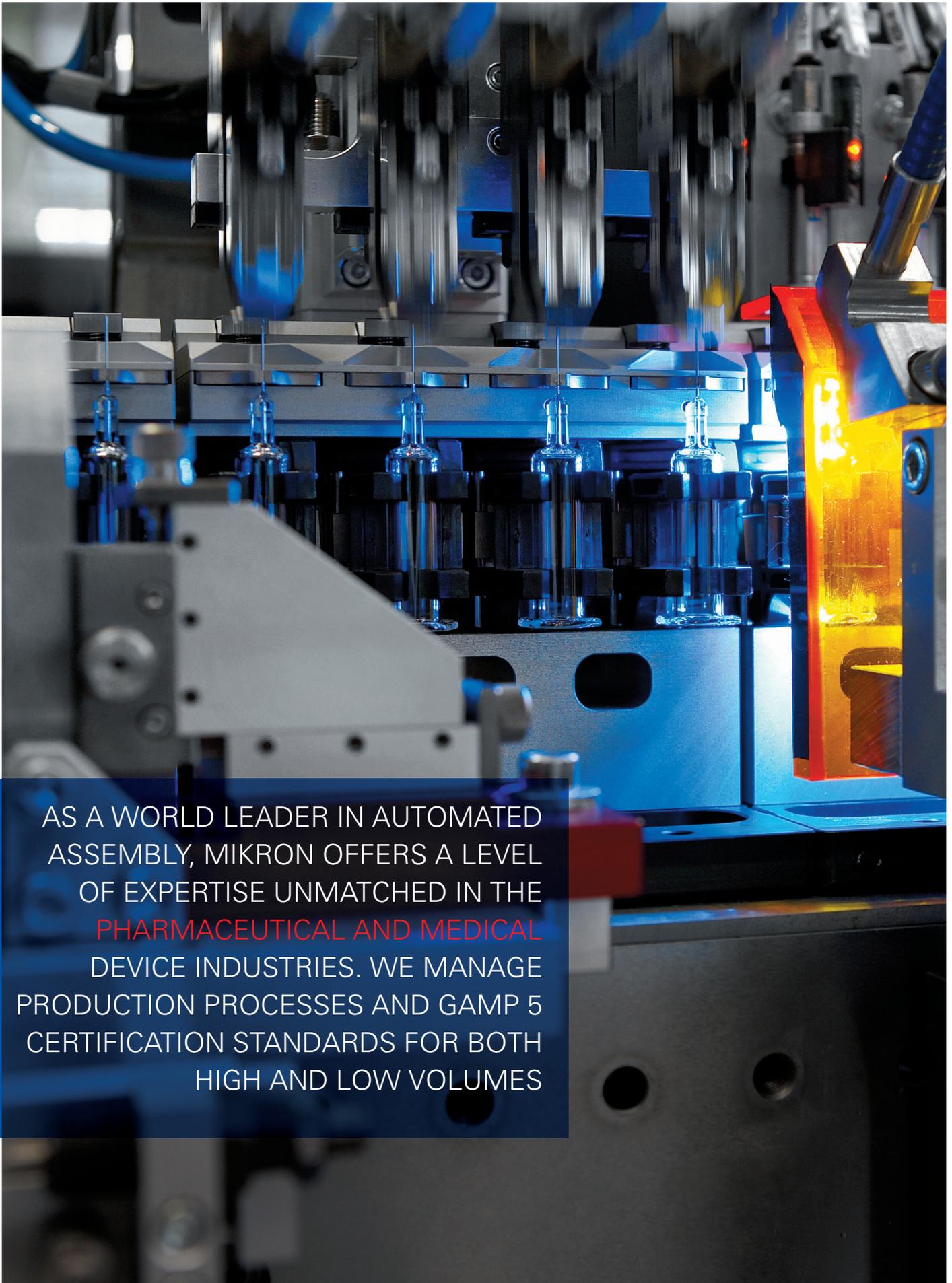
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AS A WORLD LEADER IN AUTOMATED ASSEMBLY, MIKRON OFFERS A LEVEL OF EXPERTISE UNMATCHED IN THE PHARMACEUTICAL AND MEDICAL DEVICE INDUSTRIES. WE MANAGE PRODUCTION PROCESSES AND GAMP 5 CERTIFICATION STANDARDS FOR BOTH HIGH AND LOW VOLUMES



THE LAST WORD IN ASSEMBLY SOLUTIONS JUST GOT EVEN BETTER

The G05, Mikron Automation’s flagship assembly solution, has been unveiled this year in an improved version. Here, Markus Werro, Head of Development, and Jean-François Bauer, Head of Marketing and Business Development at Mikron Automation, describe the full range of advantages offered by this new improved version.

A truly incredible development! The Mikron G05 system (Figure 1), a symbol of Swiss precision, modularity and profitability, has just been honed further with a series of innovations. The result? A more efficient assembly solution than ever before, capable of satisfying the increasingly exacting demands of leading industries including the pharmaceutical and medical sectors. The system has enabled Mikron Automation to consolidate its position as world leader in assembly and testing solutions for handheld products.

As Markus Werro explains, the innovations introduced by the leader in high-performance assembly solutions relate to three main areas. “Ergonomics have been optimised, new functions specially designed for the pharmaceutical and medical industry have been added, and finally, a whole series of improvements has been implemented on the control systems.”

IMPROVED COMFORT AND SAFETY

The first development, which users will particularly appreciate: door ergonomics. From now on, each cell will incorporate a specialised



Figure 1: The assembly solution Mikron G05 – Performance and Quality

counterweight and locking system which allows staff to handle the doors easily, with minimum effort and in complete safety. Another area of improvement has been the reduction in the sound level of the cell, the conveyors and the pallets, achieved by using new materials.

METHODS OPTIMISED FOR THE PHARMACEUTICAL AND MEDICAL INDUSTRY

Second development: Good Manufacturing Practices (GMP) and working methods. “For the pharmaceutical industry, the medicinal product is included in the production process,” explains Werro. “However, because the same platform is used to produce several product variants, the risks of contamination are significant when switching from one product to another. This means thorough cleaning is required between each process, which can be very time-consuming. Reducing the platform’s cleaning times increases its efficiency and the return on investment.”

The cleaning method has been made easier to allow the customer to switch from one production process to another more quickly. How? Firstly, thanks to a stainless steel wall which separates the work area from the rest of the frame. Inclined planes have also been inserted in the cell door, and the height of the door has been lowered to improve accessibility (see Figure 2).

Yet the added value of the G05 is not just technological: it also in particular affects the working and design methods. To optimise these methods, each Mikron Automation production site has a team of experts responsible for the medical qualification process. This team trains and monitors the project teams in charge of designing the assembly solution, so that, right from the start of the project, they can take into

account the validation processes the platform must undergo. The set of documents, which is given to the customer, is an essential tool when the US FDA or other regulatory body audits the customer. This saves a huge amount of time.

CHECKING SYSTEMS: USER COMFORT IS PARAMOUNT

Special attention was devoted to the platform’s checking systems. In terms of hardware, the electrical wiring has been redesigned. This is in line with the tightening of safety and electrical standards seen in recent years. The assembly system has also been designed to reduce electromagnetic pollution and comply with EMC standards.



Jean-François Bauer
Head of Marketing & Business Development

T: +41 32 843 11 11
F: +41 32 843 11 12
E: Marketing.mbo@mikron.com

Mikron Automation
Route du Vignoble 17
CH-2017 Boudry
Switzerland

www.mikron.com/automation



Figure 2: Mikron G05 for Pharma/Medical application – Easy cleaning due to physical separation of the assembly area, covered process and handling stations.

On a software level, crucial improvements have been made to the HMI (Human-Machine Interface) on G05 assembly platforms controlled by a Siemens S7 or Allen-Bradley PLC. The new highly intuitive and ergonomic interface incorporates the graphical advantages of a PC interface in PLC architecture (see Figure 3).

The world leader did not do things by halves when designing this new interface. Mikron Automation sought help from its customers and a world expert in HMI design to ensure users' wishes were taken fully into account. The result is a greatly simplified display allowing the production operative working on the assembly system to navigate easily from one piece of information to another.

The G05's new HMI is also richer in terms of data. It allows all important information on the station to be decrypted and provides an overview of the entire process: number of stations, development by station, statistics for completed parts and errors, etc. Finally, operation times have been reduced – a major improvement: the mechanics can adjust and modify the production process directly from the HMI, without the need for support from the programmer. This makes them more independent.

G05: THE BENCHMARK FOR ASSEMBLY PRODUCTION SOLUTIONS, NOW AND ALWAYS

The latest improvements made to the G05 continue the success story of this Swiss-made assembly solution. As 2002's successor to the legendary Flexcell, the Mikron G05 earned a name for itself on the market thanks to its exceptional qualities, as Markus Werro and Jean-François Bauer both like to recall.

The G05 stands out from competitors' solutions by virtue of its incredible production times. With certain traditional machines requiring almost 12 months between the design stage and the actual start of production, the G05 is a true record-breaker.

"In 2009, at the height of the threat from H1N1 flu, we had to deliver a solution in

just 12 weeks! Sixteen weeks later, following the qualification process, production of the first parts could begin. No-one operating today could achieve so much," asserts Jean-François Bauer. This speed is a crucial advantage in an increasingly fast-paced world, where product life cycles are becoming shorter and legal norms are constantly imposing new changes.

UNPRECEDENTED MODULARITY

And the secret to such speedy production? Modularity. Markus Werro explains: "Instead of developing a unique, A-to-Z solution for each project, Mikron Automation took a gamble nine years ago to design a standardised and reusable platform that could be rapidly configured for each new customer project or reconfigured to allow an existing product to be modified."

In real terms, the G05 consists of a series of "building blocks": a highly robust and stable base frame, a process module supporting standardized handling units, standard conveyors and standardized basic software. The rest is completely customizable: specific processes and supply systems can be integrated and additional software is incorporated to suit the specifications and customer requirements. "Our customers know that we will not just deliver a machine", continues Markus Werro, "we will supply them with a tailor-made production solution".

The advantages of this modularity do not stop at the spectacular reduction in delivery times. It also results in increased efficiency and quality, incomparable flexibility and a reuse rate of up to 60 percent.

IDEAL FOR THE PHARMACEUTICAL AND MEDICAL INDUSTRY

What has made the G05 special in recent years is the way in which it has established itself as the ideal solution to respond to the stringent demands of the pharmaceutical and medical industry. The G05 takes into account the strict conditions for use in a clean room. The platform uses materials

such as high-quality aluminum and stainless steel, the conveyor belts carrying the part-holder pallets are protected and the cells are accessible to facilitate cleaning. In addition, the G05's modularity means it can be adapted more quickly to constantly changing validation standards.

G05, THE LAST WORD IN TECHNOLOGY, SUPPORTED BY THE EXPERTISE OF MIKRON AUTOMATION

In its latest incarnation, the G05 represents now more than ever before the very best in high-performance assembly solutions for large volumes. Manufactured in Boudry, Switzerland, the new G05 is the latest development in the tradition of precision and expertise established by Mikron Automation. However, as Jean-François Bauer concludes: "When you opt for the G05, you are not only choosing a technological marvel; you are also choosing comprehensive expertise and advice. In short, everything the customer needs to feel supported and understood, in the knowledge that he has purchased a production solution that will give him an edge over his competitors".

ABOUT MIKRON AUTOMATION

Mikron Automation, the leader in assembly solutions.

Mikron Automation is one of the world leaders in automation solutions. With over 100 years' experience, including 35 years in the field of assembly, this Swiss company is committed to constant innovation in order to supply the very best solutions and services to major players in the pharma/medical, automotive, electrical/electronics and consumer goods industries. Mikron Automation employs over 400 workers worldwide and has premises in Boudry (Switzerland), Denver (United States), Singapore and Shanghai (China).

SPECIALISING IN THE QUALIFICATION OF PHARMACEUTICAL AND MEDICAL PROJECTS

Certain industries, such as the pharmaceutical and medical industry, are subject to particularly stringent legislation. The production processes must be validated according to strict rules.

To satisfy these specific demands, Mikron Automation guarantees right from the design stage that its platforms conform fully to the latest certification standards in force (GAMP5, GMP, 21 CFR part 11 compliant), and provides auditors with all the necessary documentation. Significant savings in terms of time and costs.



Figure 3: User-friendly HMI – A simplified display allows the operators to navigate their information screens easily.



MannKind Corporation™

PULMONARY DRUG DELIVERY - SIMPLIFIED

Following up on their article that appeared in ONdrugDelivery last November, Andrea Leone-Bay, PhD, Vice-President, Pharmaceutical Development; Chad Smutney, Senior Director, Device Technology; and Joseph Kocinsky, Senior Vice-President, Pharmaceutical Technology Development, all of MannKind Corporation, detail specific advantages and applications of the company's pulmonary formulation technology and inhaler devices. Also described are proprietary inhalation product development technologies and processes that speed time to market for inhalable drugs – both for local and systemic delivery.

The route of administration is critical for any medicine. For decades, the most common dosage forms were either oral or for injection. Patients generally preferred oral therapies over injected medications because oral delivery is non-invasive and convenient. Based on this preference and advances in drug delivery technologies, several other non-invasive dosage forms, including orally inhaled dry powders, have been developed and offer excellent alternatives to the more traditional “pills and needles”.

Drug delivery by inhalation presents unique advantages that are not available with other modes of administration. For example, the large surface area of the lung (about the size of a tennis court) provides efficient drug absorption. Additionally, inhalation is simple and convenient, particularly with the newest innovations in inhaler design and function. Even the challenges previously inherent in developing inhalation products are nearing resolution. The concept of translational medicine has been introduced into the development of inhalation products with the advent of advanced inhalation development technologies that directly link the bench and the bedside.

Self-administered inhaled drugs were initially used only to treat pulmonary diseases, like asthma, where direct delivery to the site of action provided a clear advantage. However, inhalation dosage forms have evolved significantly over the past decade expanding their use in a wide spectrum of disease therapies ranging from pulmonary indications routinely treated with inhaled medicines (asthma, cystic fibrosis, chronic obstructive pulmonary disease) to novel applications of the inhalation route to

treat systemic diseases (irritable bowel disease, schizophrenia, migraine, diabetes, and obesity).

Notable recent progress in the inhaled drug arena for non-pulmonary indications includes: the development of Staccato® Loxapine for the potential treatment of schizophrenia (Alexza Pharmaceuticals, Mountain View, CA, US); Afrezza® for the potential treatment of diabetes (MannKind Corporation), Levadex™ for the potential treatment of migraine (MAP Pharmaceuticals, Mountain View, CA, US), and Inavir®, an anti-influenza treatment launched by Daichii Sankyo (Tokyo, Japan).

MannKind Corporation develops pulmonary drug delivery systems that combine a dry powder formulation with convenient, patient-friendly devices. Transitioning combination products from concept to clinical practice is simplified by innovative technologies that have been developed by MannKind.

FORMULATION TECHNOLOGY

Development of formulations for dry-powder inhalation combination products requires some key considerations including stability and particle architecture. Drug stability should be evaluated in both crystalline and amorphous particles. The particle engineering technology itself must have the capacity to produce powders effectively and efficiently with any desired particle-size range to accommodate a variety of therapies. Finally, the manufacturing technology should be scalable and cost effective.

MannKind's formulation technology is applicable to both small-molecule therapeutics as well

Dr Andrea Leone-Bay
Vice-President, Pharmaceutical Development
T: +1 203 796 3421
F: +1 203 798 7740
E: aleone-bay@mankindcorp.com

Mr Chad Smutney
Senior Director, Device Technology

Mr Joseph Kocinsky
Senior Vice-President,
Pharmaceutical Technology Development

MannKind Corporation
One Casper Street
Danbury, CT 06810
United States

www.mannkindcorp.com

as proteins and peptides. The Technosphere® technology is based on a novel and inert small molecule excipient that forms particles appropriately sized for inhalation into the deep lung without the traditional requirement for subsequent processing (such as milling, blending, sizing, etc).¹⁻⁶ These dry-powder formulations can be prepared from a wide range of drugs and demonstrate several distinct advantages over conventional dry powder inhalation formulations.

As an example, standard dry-powder formulations are generally sugar-based (e.g. lactose, mannitol). In most cases, the sugar is blended with micronised drug powders. This process produces heterodisperse particle mixtures with a wide size distribution that necessitates downstream processing to reduce and harmonise particle size. Unfortunately, even after milling, sizing, blending, and micronising, the final powders remain heterodisperse with poorly controlled and nonspecific particle morphology and size.

By contrast, Technosphere powders are monodisperse and low density with particle morphology and size fixed during particle formation by either controlled crystallisation or spray drying. The resultant powder comprises a narrow particle size distribution with a mean geometric diameter of about 2 µm and a very rapid dissolution profile. The ability to control particle size during particle formation facilitates the preparation of particles in a specific size range. This particle engineering capability can be used to prepare small particles for inhalation into the deep lung or larger particles for deposition in the upper airways.

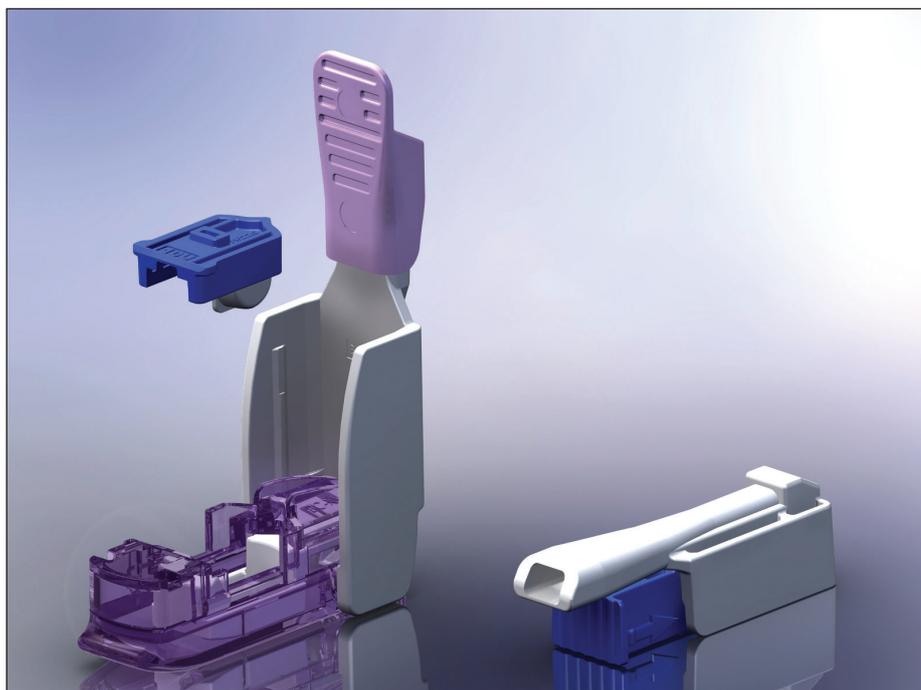


Figure 2. Re-usable Dreamboat inhaler (left) and a single-use, disposable Cricket inhaler (right).

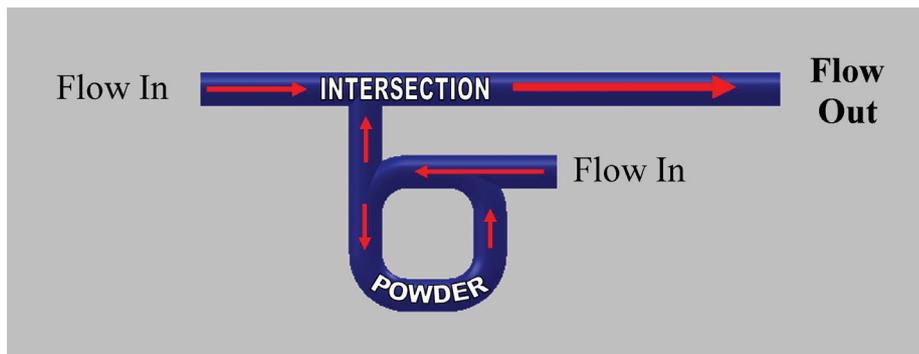


Figure 1. MannKind's common flow path.

DEVICE TECHNOLOGY

Powder delivery to the patient occurs with easy-to-use and patient-friendly dry-powder inhalers designed for convenient self-administrations. MannKind has developed two device formats, a re-usable device called Dreamboat™ and a single-use, disposable device called Cricket™, to meet therapeutic, patient, and/or manufacturing needs. Uniquely, the inhalers utilise a high resistance design enabling low in-use flow rates that reduce powder deposition in the throat and promote deep lung powder deposition for ease of patient use.⁷

At the foundation of MannKind's advanced inhalation development capabilities lies the fact that both Dreamboat and Cricket device formats share a common flow path (shown in Figure 1). This feature makes powder delivery similar and predictable. As a patient inhales, two flow inlet streams converge simultaneously. The first inlet stream lifts the powder from a containment region to fluidise it and deliver it into a second

by-pass inlet stream. The intersection of these two inlet streams breaks up the fluidised powder into particle sizes suitable for inhalation. The de-agglomerated powder then travels down a mouthpiece outlet and into the mouth. The powder dispersion occurs rapidly and early in the patient's inhalation manoeuvre.

Tuning of the flow path to meet a particular patient population or formulation need is readily achieved by adjusting elements of the straightforward schematic (Figure 1). For example, lowering the flow resistance can make more flow available to improve performance for formulations that require more de-agglomeration or for patients with lower inhalation capacity. Importantly, the patient's breath alone powers the device. This breath-powered mode of delivery is very patient-friendly because the traditional co-ordination between device activation and patient inhalation has been eliminated.

The Dreamboat (re-usable) and Cricket (single-use, disposable) device formats are shown in Figure 2. Each device is pre-metered with up to 15 mg of Technosphere inhalation powder making dose selection for patients uncomplicated. Dose is controlled during product manufacture by pre-metering the required quantity of powder into the cartridge (Dreamboat) or device (Cricket). Both of these dosing formats are designed for single use.

To use the Dreamboat device, patients select a cartridge, place it in the inhaler, inhale the contents, and discard the cartridge. Dreamboat's intuitive design features five easily molded plastic components making it manufacturing friendly. Yet more simply, the Cricket requires the patient to advance a button, inhale the contents, and discard. It features two easily molded plastic parts that merge the Dreamboat inhaler and cartridge together.

ADVANCED INHALATION PRODUCT DEVELOPMENT TECHNOLOGIES

The development of dry-powder/device combinations for inhalation products has historically been viewed as complicated, challenging,

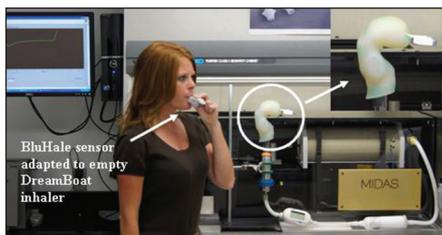


Figure 3. Device emptying assessment with anatomical and physiological aspects.

and limited to pulmonary diseases. MannKind's inhalation development processes are designed to simplify inhalation product development to make the inhalation route of administration one that is routinely considered early in the development of any drug. With this intent in mind, and in addition to MannKind's formulation and device combination, MannKind is also pioneering advanced inhalation drug development technologies that can reduce both the cost and time required to bring new products to commercialisation. These innovations can transition pulmonary drug delivery candidates rapidly into patient-friendly medicines in a translational medicine format.

The development of an inhalation drug candidate begins with the identification of a proposed therapeutic regimen. Chronic or frequent administrations may be more suited to the Dreamboat device because it is re-usable. Depending on the powder formulation and clinical indication, this device can be used for periods ranging from 15 days to three months, without cleaning or maintenance, and then discarded.

Conversely, the Cricket device is intended for short duration, time of need, or infrequent therapy administrations because this device is disposable after a single use. Prototype powder formulations are made and filled into one of the device formats for initial performance screening. Several metrics are used including

mass percent powder emptying from the device, discharge duration, and geometric particle size of the dispersion. These metrics are key indicators of device efficiency, and they are particularly connected with all aspects of patient use. MannKind therefore adopts a patient-forward approach during all its evaluations.

During the assessment for mass percent emptying, patient-mimicked physiologic inhalation efforts are created using MannKind's MIDAS (MannKind Inhalation Data Automated Simulator) and BluHale® systems (Figure 3). MIDAS is a linear servo driven syringe pump with a customised algorithm for replicating patient inhalation efforts. It is used in combination with an anatomical model to replicate a patient's upper airway (mouth and throat). BluHale is a compact, wireless pressure profiling technology used to capture and transmit data from a patient's inhalation effort. It features a small, discreet, electro-acoustic sensor that outputs a signal calibrated to pressure.⁸

During testing, a BluHale sensor is adapted onto the selected inhaler format to transmit a patient inhalation effort without drug administration. An anatomical model is placed in series with MIDAS and a second inhaler containing pre-metered dry-powder formulation is connected. As a volunteer inhales through the empty inhaler, BluHale transmits the *in-vivo* effort to MIDAS which in turn discharges the powder (from the inhaler with drug) through the *in-vitro* anatomical model. At the base of the anatomical model, a clear tube with filter paper is provided to allow observation and capture of the powder passing through the upper airway.

Insights into throat deposition and discharge time are made qualitatively and quantitatively. Device emptying is assessed gravimetrically after it is removed from the anatomical model. Uniquely, formulation/device combinations

can be assessed with any desired inhalation effort to probe device emptying efficiency. Excipients may be added or their ratios adjusted to improve emptying of the powder from the device. Additionally, device and particle geometry may be altered slightly to promote greater powder fluidisation from the device.

In parallel to the device-emptying assessment, MannKind uses a laser diffraction instrument, Helos (Sympatec, Clausthal-Zellerfeld, Germany), to assess geometric particle sizes within the emitted powder plume. A novel adaptation to the instrument's standard inhaler test module (Figures 4 & 5) was developed to improve test integrity, consistency, and resolution.⁹

Similar to a discharge from a pressurised metered-dose inhaler (pMDI), the inhaler is placed in a chamber where positive pressure is used to propel the powder from the device. The discharged plume traverses an ambient zone where it is scanned by the instrument's laser (Figure 6). This approach overcomes pitfalls associated with laser diffraction methodology such as double counting of particles and reported measurement durations which are not in alignment with discharge times.

This novel adaptation results in a high-throughput screening methodology with sufficient resolution to optimise inhaler and formulation combinations. Minor shifts in geometric particle size are easily measured to ensure that optimal powder de-agglomeration is achieved. Interestingly, the equipment is linked with MIDAS to quantify the effects of inhalation effort on particle size and discharge duration. Similar to the emptying, both formulation and device geometry adjustments can be made to achieve the desired particle-size distribution.

A preferred formulation/device combination is identified based on this *in vitro* data. Then, an initial clinical study is conducted to define the

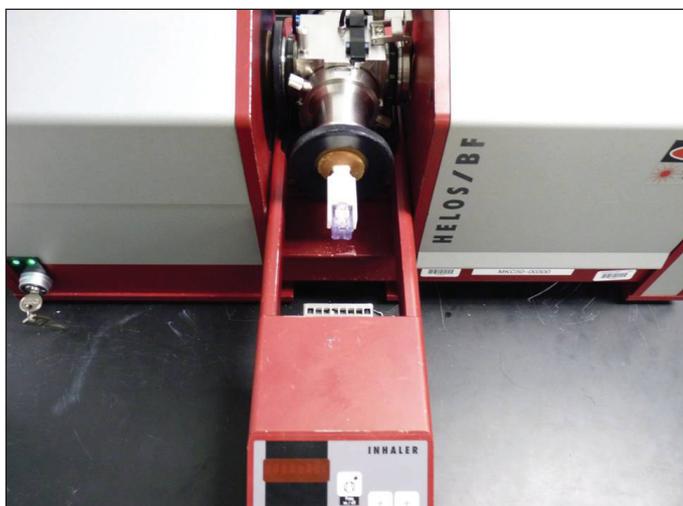


Figure 4. Laser diffraction instrument shown with standard inhaler module.



Figure 5. Laser diffraction instrument shown with MannKind's inhaler module.

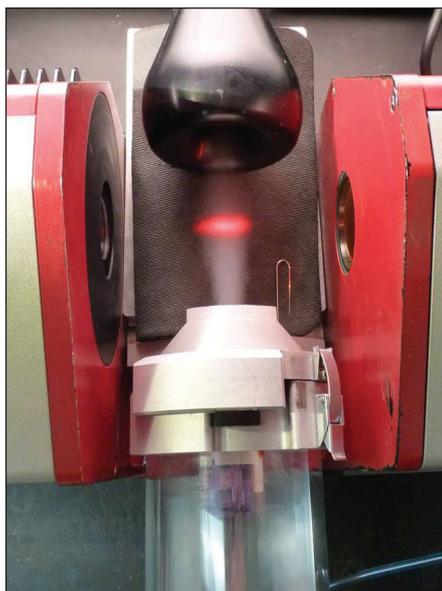


Figure 6. Discharged Dreamboat plume with laser scan using MannKind inhaler module.

performance of this prototype inhalation product in a representative patient or healthy normal volunteer population using BluHale. The data obtained from the study are used to characterise *in vivo* dose effects. Taking advantage of the fact that sound generally emanates in all directions, the BluHale sensor is placed outside the inhaler flow path.

This configuration allows capture of inhalation data during dose administration without affecting the patient/device interface. An interactive screen receives the BluHale transmission and enables users to visualise their inhalation effort in real time. These data facilitate device “tuning” to meet the needs of the specific patient population (Figure 7).⁸ When a clear and readily measured clinical bio-marker is available, pharmacokinetic data are used to establish a relationship, or lack thereof, between dose response and user technique. BluHale can also serve to eliminate unwanted sources of variability associated with varied inhalation technique. Taken together, using BluHale to profile patient inhalation technique helps define the design space for the pulmonary system within the intended patient population. This approach to comprehensive understanding for all aspects of the inhaled delivery helps advance the drug candidate quickly along the development timeline.

CONCLUSION

Integration of formulation/device technologies with advanced product development capabilities, translates laboratory bench ideas, designs, and concepts directly to bedside patient medications. Formulation selection combined with device optimisation can be accomplished in

a laboratory setting using realistic patient inhalation profiles. Bringing this already advanced formulation/device combination to the clinic has the clear potential to maximise development efficiencies for inhalation products across a wide arena of clinical indications. Inhaled medicines are no longer limited to the treatment of pulmonary disease.

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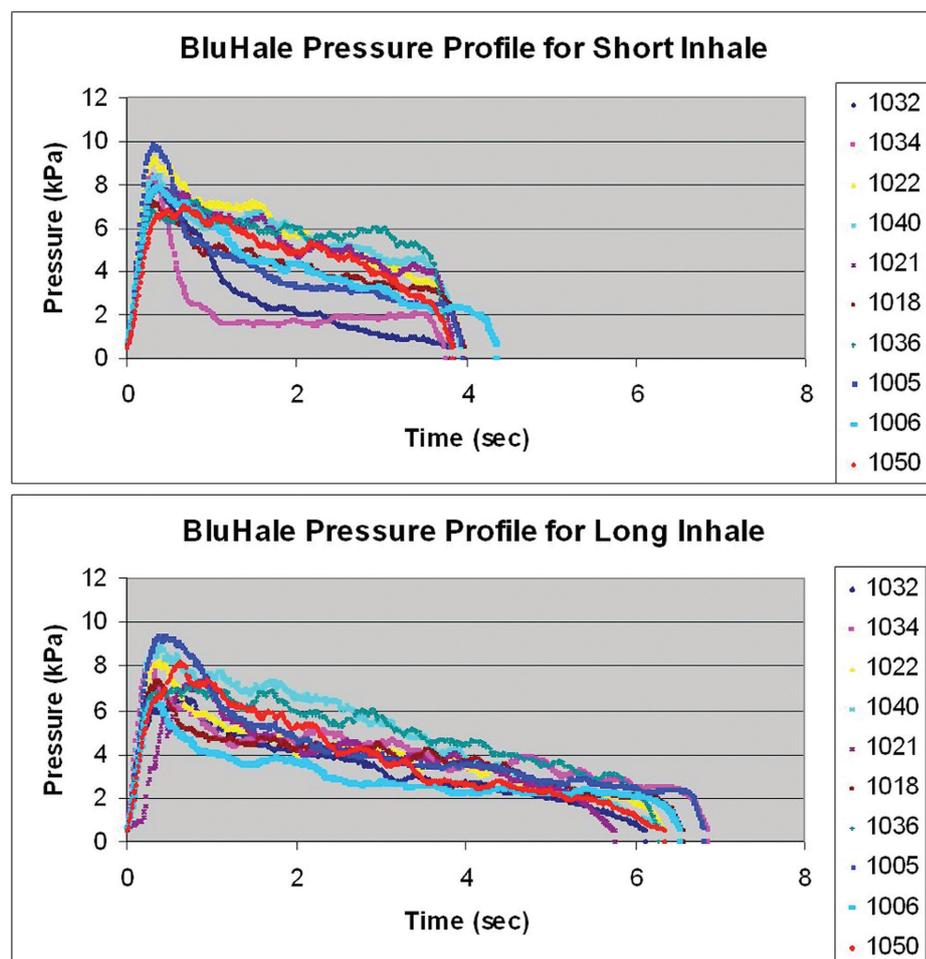


Figure 7. Dosing profiles for subjects inhaling with short and long durations.



LASER DIFFRACTION AND AUTOMATED IMAGING: COMPLEMENTARY TECHNIQUES FOR DRY-POWDER INHALER DEVELOPMENT

In this article, Deborah Huck, PhD, Product Technical Specialist, Morphological Imaging Systems; Paul Kippax, PhD, Product Group Manager, Micrometrics; Anne Virden, PhD, Product Technical Specialist, Diffraction, all of Malvern Instruments, and Janne Raula, PhD, Senior Research Associate; and Professor Esko Kauppinen, PhD, Teicos Pharma, Inc (Espoo, Finland), explore the value and complementary nature of laser diffraction and imaging when engineering DPI formulations to meet defined performance targets. Taking the example of applying a particle coating during the development of a carrier-DPI formulation, the authors show how the real-time particle sizing capability of laser diffraction, in combination with the shape analysis provided by automated imaging, promotes efficient optimisation.

The delivery of dry powders to the lung, and increasingly to the nasal cavity, is a topic of considerable interest in the pharmaceutical industry. Both targets offer a large surface area for absorption and both provide an opportunity for drug delivery in a manner that avoids the digestive environment of the gastrointestinal route and also the patient acceptability issues associated with intravenous administration.

Dry-powder inhalers (DPIs), because they are not reliant on the use of a propellant, present an environmentally friendly alternative to metered-dose inhalers and require little or no patient co-ordination since delivery is triggered by the patient drawing breath. Stability is an important advantage of dry formulation in both pulmonary and nasal delivery.

Developing successful DPIs, a device and formulation that together provide reliable, reproducible and convenient drug delivery, is a complex, expert task. The formulation challenge centres on engineering a powder blend that can be dispersed to a respirable size, typically less than five microns, solely by the inhalation effort of the patient. One solution is to use “carrier” particles to improve both flow and dispersion behaviour, but the alternative “carrier-free” option offers an important patient benefit: a reduction in the amount of material deposited in the mouth and

throat through sedimentation and impaction. Minimising the cohesive forces between fine active pharmaceutical ingredient (API) particles that lie in the sub-five-micron range is essential for the development of carrier-free formulations.

DEVELOPING CARRIER-FREE DPI FORMULATIONS

To target the lung, an API must have a delivered particle size of around 5 µm or less. However, below 10 µm, the strength of inter-particle forces of attraction rises exponentially, dramatically increasing the likelihood of agglomeration. Modifying the properties of the fine API particles to reduce the cohesive forces between them is therefore essential for successful carrier-free delivery.¹ One approach is to reduce the contact area between particle surfaces, for example by increasing surface roughness. An alternative is to reduce particle surface energy.²

Leucine has been shown to aid aerosolisation when present on the surface of drug particles^{3,4} and recent studies have demonstrated the ability of very small L-leucine crystals to enhance the flow and dispersion behaviour of API particles.⁵ In the study described here, the aim was to investigate links between the proportion of L-leucine applied, the resulting changes

Dr Paul Kippax
Product Group Manager,
Micrometrics
T: +44 1684 892456
F: +44 1684 892789
E: paul.kippax@malvern.com

Malvern Instruments Ltd
Enigma Business Park
Groewood Road,
Malvern
Worcestershire, WR14 1XZ
United Kingdom

www.malvern.com

in particle shape and surface topology, and dispersion behaviour in a DPI.

Experiments were carried out using three samples of salbutamol sulphate (Alfa Aesar, Germany) coated with different proportions of nanosized L-leucine crystals (Fluka, Switzerland) via a process of physical vapour deposition (PVD) in an aerosol flow reactor.⁶ For comparison, a commercially available micronised salbutamol sulphate (MSS; Gamprex, Italy) sample was also characterised. Throughout this article the descriptors of the coated samples reflect the relative proportions of salbutamol sulphate (S) and L-leucine (L) present. For example, sample S97L03 contains 97% salbutamol and 3% L-leucine. Laser diffraction and automated imaging were applied to investigate the properties and behaviour of all four samples.

IMAGING STUDIES: OBSERVING THE LINK BETWEEN COATING AND SURFACE STRUCTURE

The particle morphology of each of the samples was assessed using an automated image analysis-based particle characterisation system (Morphologi G3, Malvern Instruments). Figure 1 shows circularity data for the four samples; circularity being a normalised descriptor of particle form. Particles with circularity close to one are those with a 2D projection that is an almost perfect circle, while circularities closer to zero indicate a more irregular shape.

The results show that for the coated samples circularity decreases with increasing L-leucine content: samples with just 3% L-leucine have a circularity close to one while those containing 18% L-leucine have a more complex less circular shape. Opposing this trend the MSS sample exhibits the lowest overall circularity value, with images indicating that it contains a significant number of elongated particles (see figure 1). SEM observations (not shown) confirm that the four samples have very different particle shape and surface topography.

USING LASER DIFFRACTION TO INVESTIGATE DRUG DELIVERY CHARACTERISTICS

The aerosolisation properties of both the coated and uncoated samples were assessed using a laser diffraction system (Spraytec, Malvern Instruments). Tests were carried out at 30, 60 and 90 L/min, for each formulation using a passive inhaler device (Monohaler, Miat SpA, Italy). Both entrainment rate and dispersed particle size were studied as a function of flow rate. Total emitted mass was measured gravi-

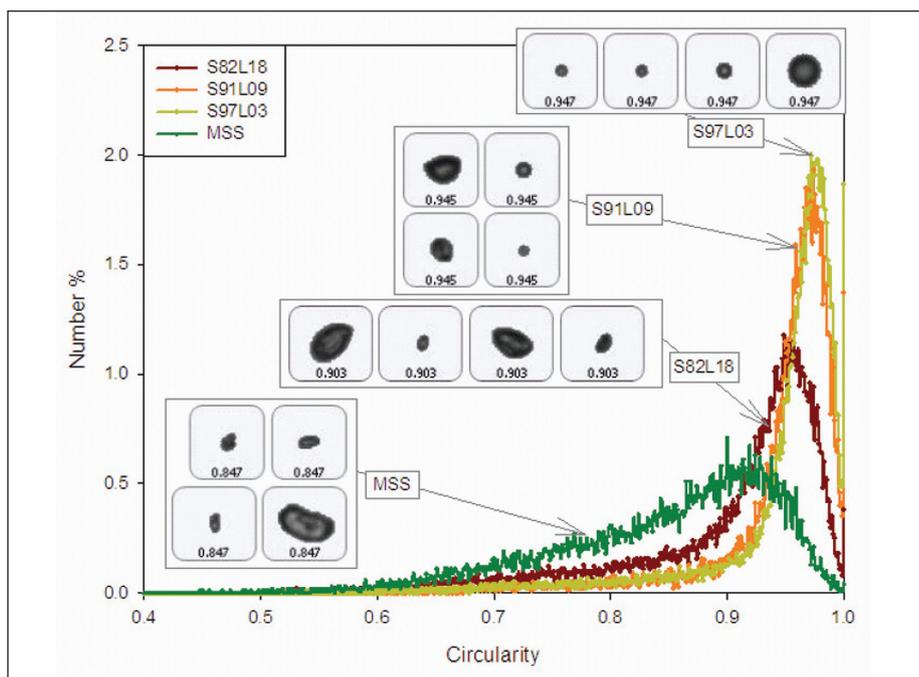


Figure 1: Circularity distributions for coated and uncoated samples of salbutamol, including example images of particles representing the mean circularity values.

metrically by weighing the inhaler and capsule before and after each actuation.

The recorded data show good, reproducible dispersion to a respirable size at each flow rate for all three coated samples (Figure 2). The proportion of the emitted dose lying in the sub-10 μm range varies from 78-93% with the percentage of fine particles produced reaching a maximum at a flow rate of 60 L/min for all three samples. Less efficient dispersion occurs at 90 L/min.

This observation is attributed to device overload caused by rapid powder entrainment and echoes the findings of a previous study with the same device.⁷ In contrast to the coated samples, the MSS exhibits steadily improving performance as flow rate is increased.

Concentration profiles for the samples, recorded at a flow rate of 60 L/min, highlight differences in entrainment behaviour (Figure 3). With all three of the coated materials, entrain-

INTRODUCING THE COMPLEMENTARY TECHNIQUES OF LASER DIFFRACTION AND IMAGE ANALYSIS

Laser diffraction is an ensemble particle sizing technique that delivers volume-based size distributions. Non-destructive and suitable for either wet or dry samples, it is sufficiently rapid to measure particle size in real time, throughout the duration of a drug delivery event. By also measuring particle concentration within the aerosol plume, it provides detailed information about the dynamics of drug dispersion. The measurement range of laser diffraction 0.1-3000 μm comfortably spans the required size range for DPIs.

Image analysis is a particle counting technique that delivers number-based size and shape distributions. The best automated imaging systems record microscope quality images of hundreds of thousands of particles, from

0.5-10000 μm in size, in just a few minutes, to produce statistically valid descriptions of particle size and shape. A particle population can be classified according to shape, or size, or a combination of both factors, to increase experimental productivity while the retention of every image allows for visual scrutiny of particles of specific interest.

In combination, these complementary techniques deliver data that can be applied to accelerate and optimise the development of inhaled products. Laser diffraction enables the examination of powder entrainment and dispersion, while image analysis enables the study of powder structure before and after delivery. Together they allow the process of dispersion to be followed closely and understood in detail.

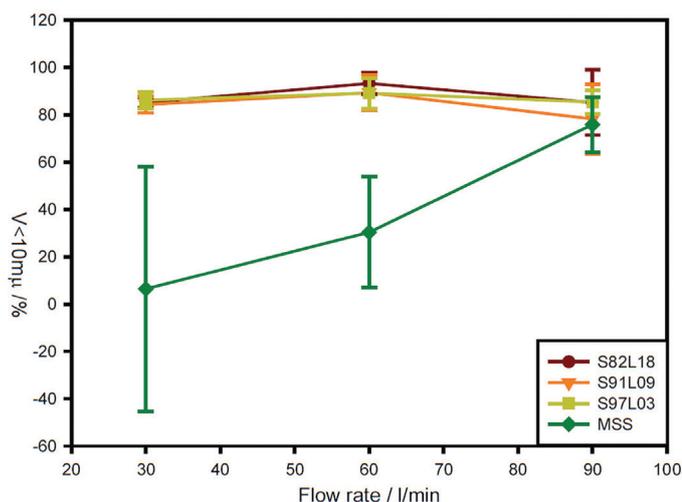


Figure 2: Flow-rate dependence of the volume of material below 10 µm in size for each formulation.

ment is rapid, giving a high initial particle concentration that is likely to be beneficial for API delivery to the lungs. Of these three samples, however, the S82L18 appears to be released most efficiently; the peak relating to the initial entrainment phase is high and the area under the curve is also markedly greater than for either of the other two coated samples, suggesting the delivery of a larger quantity of material.

Emitted mass data confirm the superior properties of the S82L18 (Figure 4). For all samples, emitted mass increases with flow rate but the S82L18 produces the highest emitted mass in each case. Variability in emitted mass tends to be higher at low flow rates, which provide relatively little energy for entrainment and dispersion of the dose.

With the baseline uncoated MSS sample there is a far less marked, initial peak in concentration, and delivery continues at a relatively steady, low concentration. Variability in emitted mass is high at all flow rates. These results suggest that break-up and dispersion of the MSS powder bed is relatively slow and inefficient.

COMPLEMENTARY TECHNIQUES, MAXIMUM INSIGHT

Combining the information provided by the complementary techniques of image analysis and laser diffraction improves understanding of the performance of the coated formulations,

encouraging successful manipulation of the variables controlling drug delivery. In this study, image analysis of the coated and uncoated salbutamol samples shows how the amount of coating applied influences particle shape. The uncoated sample has the lowest circularity and a more elongated shape. With the coated samples, circularity increases with decreasing L-leucine content, the S97L03 sample being almost a perfect sphere.

Laser diffraction data illustrate the impact of these structural changes on drug delivery parameters such as emitted dose, entrainment rate and dispersed particle size. In these tests, all three of the coated samples perform much better than the uncoated baseline which is associated with low levels of fine particles (in the sub-10 µm range), slow entrainment and flow-rate-dependent emitted dose, factors that are all suggestive of poor dispersion behaviour. The three coated samples on the other hand demonstrate good dispersion performance that is largely independent of flow rate across the range tested (30-90 L/min).

Examining the data sets for the three coated samples in more detail shows that the S82L18 dose entrains the most efficiently, yielding the highest emitted mass. So, although coating improves the characteristics of the formulation it does not appear that this is solely because more spherical particles are optimal; some degree

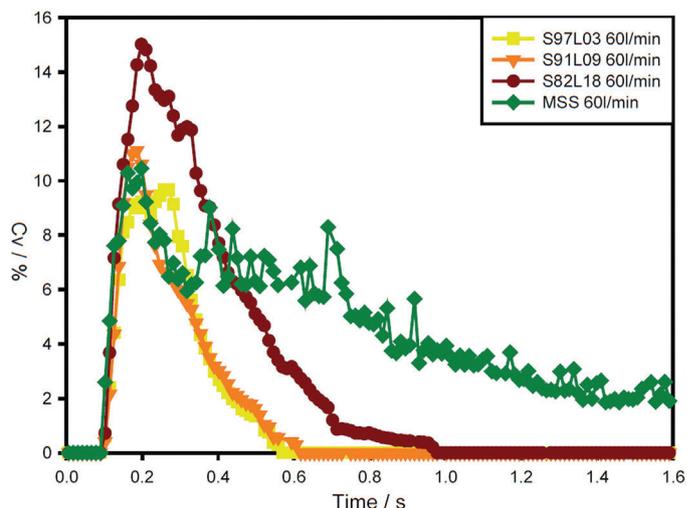


Figure 3: Concentration (Cv) profiles for S97L03, S91L09, S82L18 and MSS at the flow rate of 60 L/min.

of irregularity is clearly beneficial and surface roughness appears to play an important role.

Together the results confirm that coating the API with L-leucine nanocrystals is a viable technique for modifying particle properties to improve the dispersion of carrier-free formulations from passive DPIs. The coating process reduces the energy required to disperse the material, thereby increasing fine particle levels and improving dose-to-dose reproducibility. While all coated formulations showed a high degree of agglomerate dispersion, the properties of high L-leucine samples appear to offer particular advantages for improving delivery.

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Flow rate (L/min)	Emitted mass (mg)							
	S97L03		S91L09		S82L18		MSS	
	Average	%RSD	Average	%RSD	Average	%RSD	Average	%RSD
30	4.43	14.6	5.03	8.46	6.99	7.39	4.72	32.21
60	6.54	17.48	6.28	5.15	9	10.38	6.67	12.59
90	7.39	7.65	8.45	3.35	9.96	6.81	9.06	24.88

Figure 4: Table showing average emitted mass for each formulation at 30, 60 and 90 L/min, as calculated over three device actuations.



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VERSATILITY OF THE KHFA PMDI VALVE

In this article, Glyn Taylor, PhD, Director of Research, Cuong H Tran, PhD, Senior Research Scientist and Simon J Warren, PhD, Research Manager, all of i2c Pharmaceutical Services; Sergio Monti, Sales Manager and Gabriele Marchetti, Business Development Manager, both of V.A.R.I. SpA; and David Howlett, Director, PharmaDelivery Solutions, present a scientific study investigating the performance of the Kemp HFA valve in metered-dose inhalers under a range of conditions.

BACKGROUND UN PROJECTS

The Kemp HFA (KHFA) valve, shown in Figure 1, was investigated with a variety of HFA pMDI formulations comprising suspension, solution and a hybrid (suspension/solution) combination product containing two APIs. These formulations were evaluated as a part of United Nations (UN) co-ordinated programmes to implement the Montreal Protocol by supporting the replacement of CFC pMDI formulations with ozone-friendly replacements in certain Article 5 countries.¹ The projects were implemented in order to provide the local beneficiaries with appropriate technical support to enable the transition from CFC- to HFA-based pMDIs for specified products.

The programme comprised rapid and thorough screening of formulation constituents and hardware/packaging components to enable identification of optimal performance characteristics. In order to support the formulation development process validated and robust analytical methods were developed and

Technical support was provided on site at the beneficiaries during the production of the first commercial scale batches.

KHFA VALVE

The KHFA valve², manufactured by V.A.R.I., was used for all three formulation types developed during this project i.e. suspension, solution and hybrid combination systems.

A popular school of thought is that to get the optimum performance from MDI solution and suspension formulations two fundamentally different valve designs are required. In fact some companies actively promote capillary retention type valves for solution formulations, while others identify the benefits of 'rapid-fill/ rapid drain' type valves to best suit suspension formulations.

The KHFA valve is the result of years of development and commercial use, and offers a valve design capable of maintaining its 'prime' with solution formulations, while at the same time allowing a degree of 'rapid-fill / rapid drain' with suspension formulations. The careful selection of materials for the valve components offers a valve with very low levels of extractables. Great care has been taken to avoid some of the more reactive species that can leach from some materials, and subsequently adversely impact on the stability of more labile drugs when formulated in solution.

The result is a pMDI valve which offers superior performance with solution, suspension and hybrid combination formula-

"THE RESULT IS A PMDI VALVE WHICH OFFERS SUPERIOR PERFORMANCE WITH SOLUTION, SUSPENSION AND HYBRID COMBINATION FORMULATIONS."

were transferred to the beneficiary companies. Small-scale manufacture using batch sizes of 3,000-4,000 cans was conducted using methods that were directly scalable to commercial size batches, typically 15,000-60,000 cans.

Mr Sergio Monti
T: +39 0341 269522/23
F: +39 0341 269540
E: s.monti@lindalgroup.it

V.A.R.I. SpA
Via al mognago, 47
23848 Oggiono (LC)
Italy

www.lindalgroup.com

Prof Glyn Taylor
Director of Research
T: +44 29 2075 7865

i2c Pharmaceutical Services
Cardiff Medicentre
Heath Park
Cardiff CF14 4UJ
United Kingdom

www.i2cpharm.co.uk

Mr David Howlett
Director
T: +44 1485 60065
E: david.howlett@pharmadelivery.com

PharmaDelivery Solutions Ltd
Dalheim (3), Low Road
Grimston
Norfolk PE32 1AF
United Kingdom

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tions, without the need for design and material changes. Some of the key features of the valve include:

- Low propellant loss
- Outstanding moisture barrier protection
- Clean extractables profile
- Selection of compatible polymers
- Metering consistency
- Rapid fill/ rapid drain with prime retention
- A design able to deliver small volumes

Figure 1 shows the KHFA valve and its technical specifications.

PMDI PRODUCTS

The products developed and evaluated were; salbutamol (Salb), beclometasone dipropionate (BDP; two strengths) and a combination product of Salb/BDP. For each formulation a detailed Product Specification was devised to characterise the performance qualities comprehensively and also ensure compliance with both local and international regulatory guidelines. The performance of the developed formulations was targeted to be non-inferior to appropriate globally-marketed comparator products. The key performance parameters that were defined included total API can content, metered shot weight, mean emitted dose (at beginning and end of can life), dose content uniformity (a measure of emitted dose through can life), fine particle fraction (FPF, % of emitted dose with an aerodynamic size $<5.0 \mu\text{m}$), fine particle dose (FPD, μg API with an aerodynamic size $<5.0 \mu\text{m}$) and the level of moisture within the cans.

TEST METHODS

Precise and accurate HPLC methods were developed and validated to allow rapid and accurate quantitation of API recovered during standard tests and in-process controls (IPC). Emitted doses were determined using standard dose uniformity sampling apparatus (DUSA) for salbutamol formulations. In the case of BDP, however, during method validation it

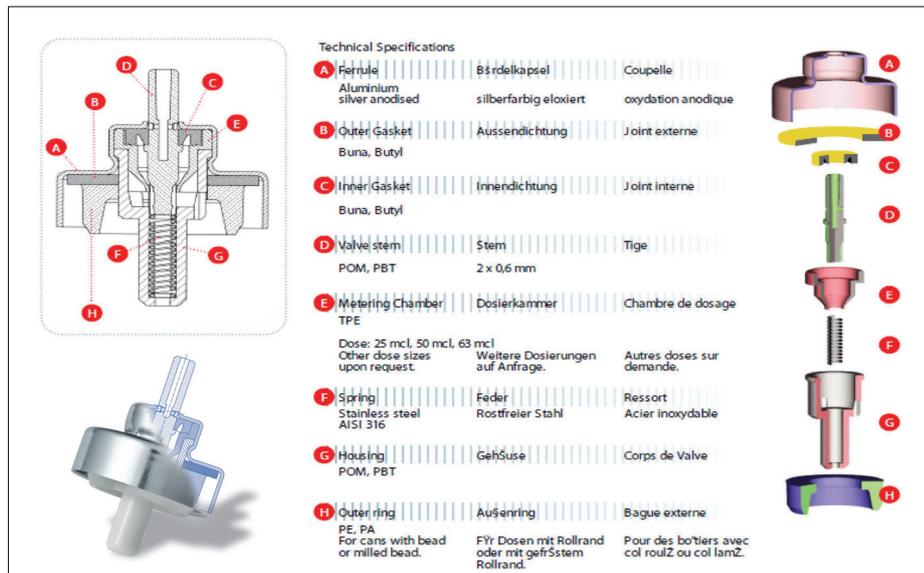


Figure 1: KHFA valve and its specifications.

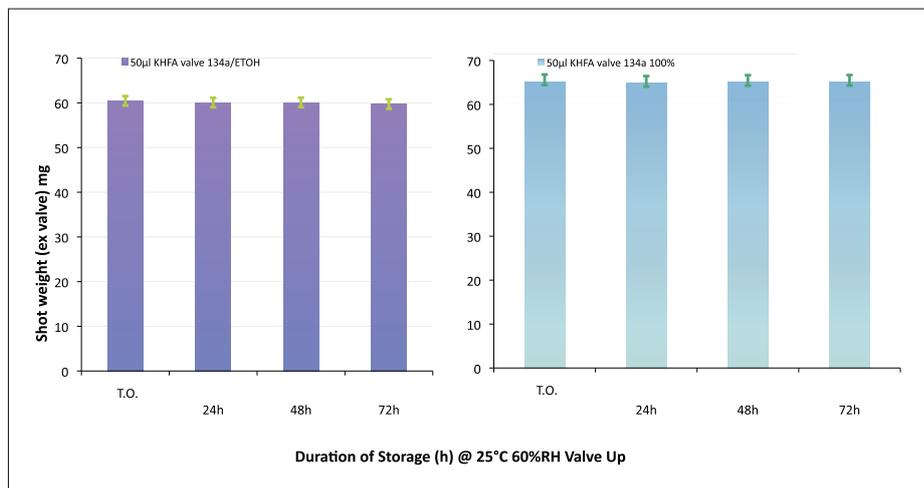


Figure 2: KHFA MDI Valve Loss-of-Prime Evaluation (LoP) following storage in valve-up position. Data shown are the mean (\pm max/min) shot weight ex valve ($n = 5$), using formulations with and without ethanol.

was determined that in order to optimise recovery of this lipophilic drug, emitted dose testing must be performed using bespoke DUSAs. Bespoke DUSAs were also used when characterising the performance of the combi product. Aerodynamic particle size assessments were conducted using the Next Generation Impactor (NGI). Tests for related substances were performed as described in the relevant sections of the British Pharmacopoeia (BP) and / or European Pharmacopoeia (EP).

Water content of the canisters was measured using a coulometric Karl Fischer Titrator fitted with an appropriate adaptor to allow direct actuation of the valve into the electrolyte solution.

During manufacture, quantitation of API for IPC was performed using validated rapid HPLC or spectroscopic methods thereby enabling rapid turnaround of samples during production.

Loss of prime (LoP) evaluations based upon ex-valve shot weight were conducted with the cans stored ($25^\circ\text{C}/60\% \text{RH}$) for up to 72 hours in valve-up position. Two model formulations were tested.

PILOT-SCALE MANUFACTURE

Pilot scale manufacture was undertaken using semi automated Pamasol equipment (Willi Mäder AG, Switzerland) comprising a propellant pump, vacuum crimper, propellant pressure filler, product filler and a five litre compounding vessel (Buchi UK Limited).

All formulations were filled via a two-stage process. All API and excipients used conformed with the requirements of the BP/EP. Salbutamol was sourced from Jayco Chemical Industries, India, and BDP was purchased from Farmabios, Italy. Propellant HFA 134a was

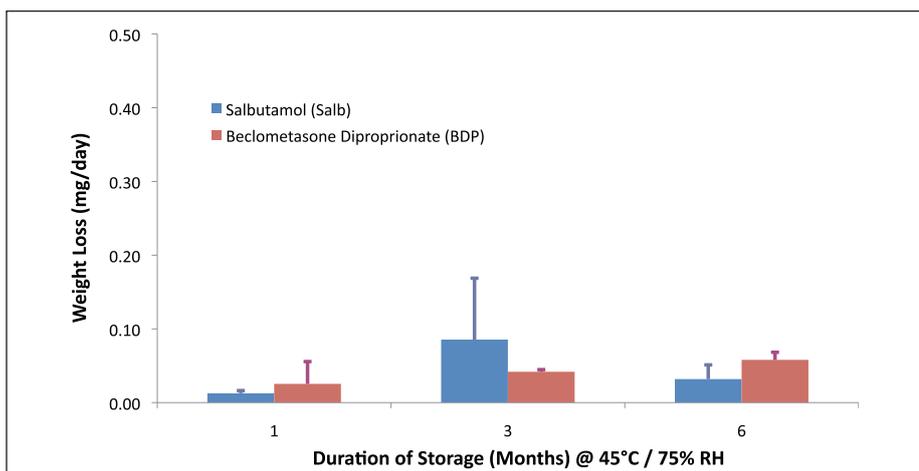


Figure 3: Average Propellant Leakage (mg/day) Following Storage at Elevated Temperature and Humidity. Data shown are mean values (\pm SD) for three batches of each formulation. Ten canisters were evaluated at each time point.

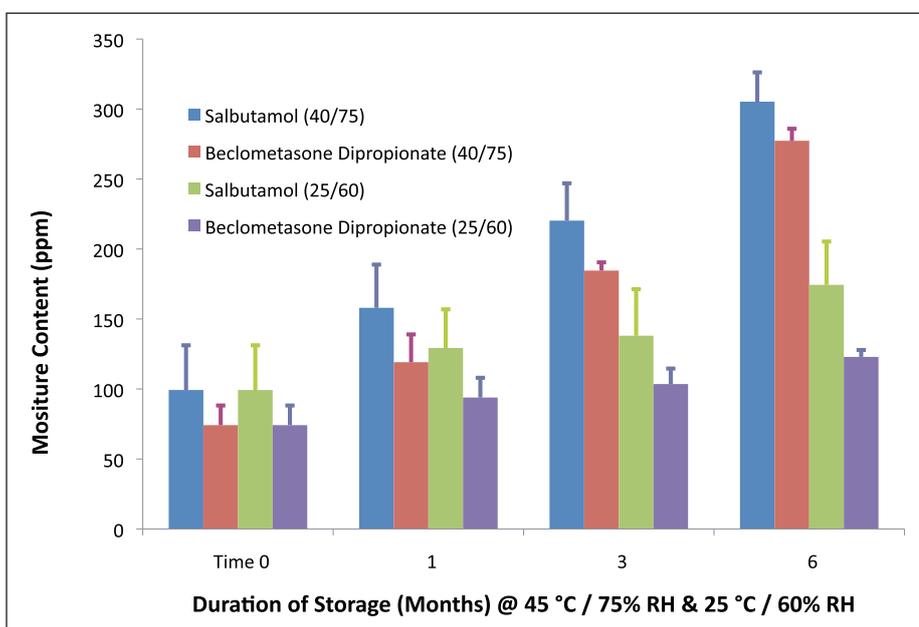


Figure 4: Moisture Content (ppm) Following Storage. Data shown are the mean values (three cans \pm SD) for three batches of each formulation.

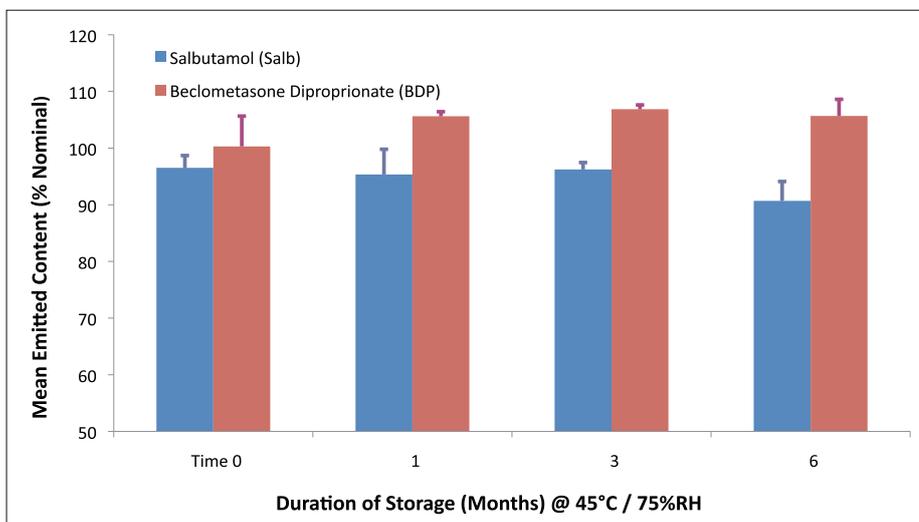


Figure 5: Mean Emitted Content (% Nominal) Following Storage at Elevated Temperature and Humidity. Data shown are mean values (\pm SD) for three batches of each formulation. Ten canisters from each batch were tested at each time point, the mean value for actuation number 5 and 200 are shown.

generously provided by Mexichem UK Ltd. 19mL aluminium aerosol cans (C128) and actuators (Nemo NMX) were generously provided by Presspart Manufacturing Ltd UK and Presspart Nemo respectively.

All cans within each batch were labelled with unique barcode identifiers. This level of control enabled individual cans to be traced to a specific stage of the filling process. As a consequence performance of the finished product could be monitored as a function of manufacturing variables such as product concentrate temperature and volume within the compounding vessel.

Small-scale batch production runs were designed to mimic commercial processes and were conducted over six-hour periods. IPC samples were taken at suitable intervals throughout the process to evaluate the effects of typical environmental changes during manufacture on the finished product. IPC checks included weight of product concentrate (suspension or solution) dispensed into cans, determination of total API in the can and total fill weight.

STABILITY STORAGE

Following a two week 'quarantine' period the products were tested to ensure compliance with the release conditions in the appropriate Product Specification. Batches complying with the release criteria were placed on accelerated stability (40°C/75% RH) and relevant room temperature conditions i.e. 25°C/60% RH and 30°C/65% RH, the weights of all cans were recorded at the start of stability testing. Cans from three batches of each formulation were stored suspended in valve-down orientation using custom fabricated stainless steel trays to ensure that all cans and valve stems were maximally exposed to the desired temperature and humidity conditions. Randomly selected cans, representative from all parts of the manufacturing batch cycle were withdrawn at the pre-defined time points – i.e. one, three and six months – and subjected to testing to ascertain that the key performance parameters remained within specification.

TEST RESULTS

Loss-of-prime results (Figure 2) showed that valve delivery, for both model formulations, was unaffected following valve-up storage (25°C/60% RH) for up to 72 hours.

Propellant losses and moisture ingress data for six months of storage in valve-down orientation at 40°C/75% RH are shown in Figures 3 and 4 respectively. These data highlight the excellent barrier protection offered by the KHFA valve.

The consistency of metered dose (% nominal dose) throughout canister life (mean of actuation five and 200) is shown in Figure 5 for both the Salb and BDP formulations for the six-month storage period.

Assessment of aerosol quality using the NGI showed that the FPF for the Salb and BDP formulations remained consistent over the six-month storage period (Figure 6). The same performance characteristics were also shown by the hybrid formulation. In all instances the FPD as determined from the NGI analysis remained within the specified limits showing the formulations to be robust and unaffected by storage conditions.

NEW BUDESONIDE/FORMOTEROL PMDI FORMULATION

A further application of the KHFA valve has been demonstrated using a novel pMDI suspension formulation.³ A proof-of-concept study was undertaken to characterise the performance of a budesonide (100 µg) / formoterol (6 µg) combination product which incorporated a non-respirable particulate excipient to stabilise the suspension.⁴ Dose delivery of budesonide and formoterol was consistent through can life in terms of FPF and FPD.

Testing of shot weight through can life was also performed to demonstrate that the additional powder load resulting from the non-respirable particulate stabilising agent did not adversely affect valve performance, this is shown in Figure 7.

CONCLUSIONS

Thorough screening and comprehensive stability evaluations of pilot-scale batches of salbutamol and beclometasone formulations utilising the KHFA valve have produced two well characterised pMDI products. The formulations have demonstrated the following attributes:

- stable at accelerated stability conditions
 - consistent emitted-dose delivery throughout can life
 - consistent delivery of fine-particle fraction / fine-particle dose
 - minimal propellant loss and water ingress when stored at elevated humidity / temperature in the absence of any secondary packaging
- formulations and pilot-scale manufacturing processes successfully transferred to commercial-scale operations.

Additionally a hybrid combination product, comprising Salb and BDP is currently undergoing rigorous assessment and one-month acceler-

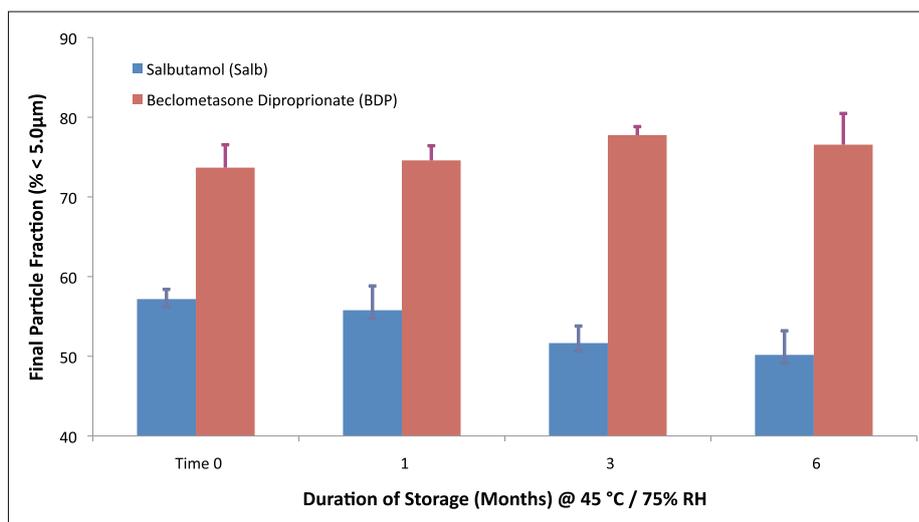


Figure 6: Mean Fine Particle Fraction (% < 5.0 µm) Following Storage at Elevated Temperature and Humidity. Data shown are the mean values (n= 5 cans, ± SD) for three batches of each formulation.

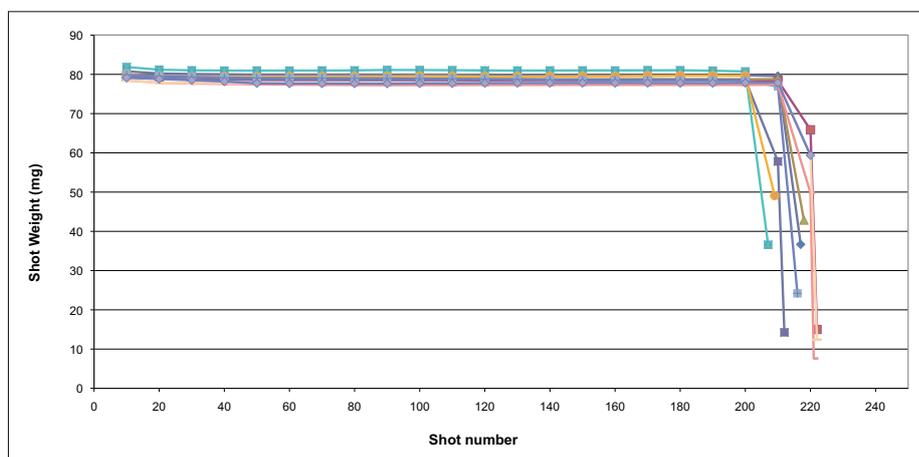


Figure 7: Shot Weight Through Can Life - Novel Suspension System.

ated stability data indicate that this system is achieving the performance criteria laid down in the Product Specification.

Finally, the KHFA valve has also been evaluated with a novel combination formulation of budesonide / formoterol which also contains a non-respirable particulate excipient. Valve performance in terms of shot weight was consistent and unaffected by the additional powder load. Furthermore, the formulation / valve permutation generated effective aerosols with appropriate FPF and FPD characteristics.

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NOVEL ADVANCES IN RAPID MANUFACTURING, DEPLOYMENT, AND DELIVERY OF INTRANASALLY ADMINISTERED DRUGS AND BIOLOGICS

In this article, Timothy Sullivan, President, Chief Executive Officer and Founder of Mystic Pharmaceuticals, provides background information on the drivers for the development of stable, nasally administered vaccines, which can be manufactured and deployed rapidly, and describes the drug delivery devices and dosage forms under development by Mystic, as well as the company's rapid form-fill-seal manufacturing processes.

INTRODUCTION

Systemic delivery of drugs, biopharmaceuticals and vaccines via the nose offers many compelling advantages including bypass of hepatic first-pass metabolism, reduced nausea and toxicity and rapid onset. Compared with parenteral administration, nasal delivery devices improve patient compliance by providing improved ease of use via either caregiver-based or self administration, as well as obviating the need for biohazardous disposal of needle sharps. These advantages are especially apparent in the case of chemical, biologic, radiation and nuclear (CBRN) threats, where nasally administered vaccines and drugs and the properly designed devices to deliver them can greatly reduce the logistical burden entailed in storage, deployment and large-scale administration. Mystic Pharmaceuticals has developed a highly adaptable platform-based nasal delivery technology that includes rapid form, fill and seal manufacturing of stabilised unit doses and highly customisable devices for precise and controlled nasal administration.

RAPID MANUFACTURING

The need for rapid manufacturing capacity for vaccines has recently emerged as a major consideration for US bio-defense preparedness policy. Lessons learned from the 2009 H1N1 flu pandemic demonstrated the need for improving

both vaccine manufacturing and fill-fit-finish production capacities. US Health and Human Services Secretary Kathleen Sebelius announced plans for major investments in Centers of Innovation for Advanced Development and Manufacturing in August 2010 with an emphasis on the development of platform based manufacturing technologies that can produce a variety of medical countermeasures and build a realistic surge capacity in the US rather than relying on foreign manufacturing.¹

While formulating vaccines for intranasal delivery is in its infancy with many vaccine manufacturers, these recent initiatives from HHS and the defense constituencies will accelerate the development of these capabilities. Federal mandates and much needed funding to advance the development of intranasal vaccines has only recently become a priority. However, there are a handful of companies that have emerged as early innovators in nasal vaccine development, including Medimmune, LLC (Gaithersburg, MD, US), Vaxin, Inc (Birmingham, AL, US), and NanoBio Corporation (Ann Arbor, MI, US), among others.

A successful transition to needle-free intranasal delivery systems for pandemic or bioterror countermeasures requires economically scalable fill-fit-finish production technology. To address this need, Mystic Pharmaceuticals has developed the MVP™ unit-dose blister production system (Figure 1).



Mr Timothy Sullivan
President & Chief Executive Officer

T: 512.918.2900
F: 512.918.2910
E: tsullivan@mysticpharmaceuticals.com

Mystic Pharmaceuticals, Inc
2006, Windy Terrace
Austin
TX 78613
United States

www.mysticpharmaceuticals.com



Figure 1: Mystic Pharmaceuticals' Versidoser™ intranasal unit dose Form-Fill-Seal production system.

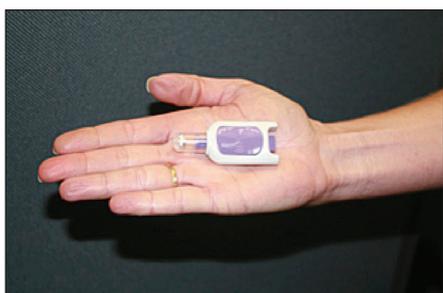


Figure 2: Mystic Pharmaceuticals' Intranasal Delivery System.

The MVP system incorporates an aseptic form-fill-seal (FFS) production process to manufacture unit-dose blisters at volumes of up to one million doses per day on a single production line. The MVP production systems employ a fully automated process for forming, filling and sealing the drug or biologic in the blister. These operations occur within a Class 100 barrier isolator to ensure sterility. Unit-dose blisters are formed using USP pharmaceutical-grade, aluminum-core, thin-film laminates. These engineered laminates provide exceptional barrier properties against oxygen, water vapour and light transmission for improved shelf stability. Additionally, MVP production systems can be configured to package live- and killed-virus vaccines, bacterial vaccines, recombinant protein- and DNA-vaccines, and small-molecule drug compounds for dose volumes ranging from 15-500 µL.

THE COMPLEXITIES OF COLD-CHAIN MANAGEMENT

Once manufactured, the proper management of immunological drugs and biologics becomes the next critical challenge. Nearly all of the current generation of vaccines designed to combat infectious diseases or bioterror pathogens – such as influenza H5N1 and H1N1, anthrax, smallpox, Ebola virus and plague – require strict adherence to cold-chain conditions throughout the product life-cycle from manufacturing, storage, transportation and through deployment and delivery.

Typically, this requires maintaining stockpiles of pre-packaged syringes in large storage facilities with transport capability at -4°C to -25°C for tens of millions of doses that are dispersed and staged across the globe in order to respond quickly in the event of a crisis.

Such daunting and expensive logistics challenges are especially burdensome for developing nations where the availability of cold-chain storage and transportation infrastructure may be virtually non-existent. Thus the cold-chain burden is the key impetus behind major development efforts to find new methods to thermostabilise drugs and biologics to reduce the logistical complexities and costs associated with storing and deploying vaccines across the globe.

Lyophilisation has been in use for decades to thermally stabilise vaccines through a freeze-drying process. Techniques such as spray drying², nano-particles³ and sugar-glass crystallisation⁴ are emerging as potentially viable alternative methods. Some compounds may be directly administered in powder form, but most first reduce the vaccine to a powder or glassy substrate that is then reconstituted back to liquid form just prior to administration. The reconstitution procedure for a lyophilised vaccine is itself a complex process, which is still typically designed for injection-based administration and requires a trained healthcare provider to ensure sterile reconstitution and accurate dose administration to the patient. Consequently, while most current thermostabilisation methods do reduce the requirements for cold-chain management, they can unfortunately complicate field deployment and remove the option for self-administration by the general population.

Intranasal delivery systems designed for safe and effective storage and self-administration facilitate rapid deployment to large populations in crisis situations while eliminating the need for biohazardous sharps disposal.

NEW PARADIGMS FOR PACKAGING AND DELIVERING THERMOSTABILISED AND OTHER MEDICINES

Novel advances in delivery technologies are upgrading the nasal route as a viable and advantageous route for systemic delivery of drugs and biologics.⁵ The possible indications range from treatments for and immunisation agents against CBRN threats such as pandemic influenza, anthrax and radiation poisoning, as well as a host of conventional drugs such as anti-emetics, anti-convulsants and hormones, and drugs for pain management, anaphylactic shock, diabetes, and migraine, to name but a few.

Non-invasive intranasal delivery can improve patient compliance within selected populations while eliminating needle sticks and biowaste. Systemic absorption via the nasal mucosa yields a rapid onset time both for therapeutics and vaccines.^{6,7} Clinical data demonstrates that vaccines can rapidly generate a local immune response within the respiratory track; a primary route of infection for airborne pathogens.^{8,9,10}

While nasal vaccine administration offers advantages, there are challenges that must be overcome. The nasal epithelium is rich in immune cells. However, protective immunity is not easily achieved because of mucociliary clearance and potentially poor absorption in individuals with nasal congestion. Vaccine developers have responded to this challenge by investigating the use of muco-adhesive agents such as chitosan and pectin to aid absorption.

In 2000, safety concerns over a nasally administered inactivated influenza vaccine were raised when patients were diagnosed with Bell's Palsy.¹¹ However, a subsequent review of the research by the US Centers for Disease Control concluded a possible Bell's Palsy risk was due to parenterally delivered inactivated influenza vaccines, reducing the probability that nasal delivery was the source.¹²

A low-cost, rapidly adaptable, and broadly applicable platform delivery technology is needed that can perform across the full spectrum of possible drug morphologies from liquid, powder, and solid to liquid and it must be capable of spanning a range of material properties. Mystic Pharmaceuticals' precision, metered, unit-dose delivery technology represents a new generation of advanced capabilities for packaging and systemic nasal administration of drugs and biologics.

Mystic Pharmaceuticals has developed two delivery platforms, the Versidoser™ and the VRx2™.

The Versidoser™ Delivery Platform (shown in Figure 2) is designed for aseptic unit-dose packaging of drugs and biologics to be directly administered as liquids (Figure 3) or powders (Figure 4). The Versidoser™ delivery device can be configured for dual-dose, bi-dose, or mono-dose regimens (see Figure 5). Further, each system can be configured for one-time use or multiple use, with replaceable tips containing the blister.

The VRx2 Delivery Platform (shown in Figure 6) is designed to package drugs or biologics that are initially in powder or solid substrate form but require reconstitution back to the liquid form just prior to administration. (Ophthalmic, otic and sublingual routes of delivery are also supported by both of these Mystic platforms.)



Figure 3: Liquid spray.



Figure 4: Powder delivery.



Figure 5: Dual-, bi- and mono-dose system configurations.

ADVANCED DELIVERY PLATFORMS

Each delivery platform comprises a customised hand-held delivery device either pre-loaded or user loadable with single or multiple aseptically packaged unit dose blisters. Each blister contains the drug or biologic material as well as a VJet™ internal piercing mechanism that also serves as the dispensing nozzle (Figure 7).

Each VJet™ is specifically optimised for the fluidic properties of the drug material such that the dispense sequence (Figure 8) results in the desired targeted spray characteristics (droplet size distribution, angle and velocity).

The VRx2™ reconstitution delivery system provides for automatic reconstitution of the drug or biologic via use of a diluent contained inside a sealed multi-chambered blister while maintaining sterility (see again Figure 6). The reconstitution procedure is virtually transparent to the user. Auto-reconstitution within the delivery device eliminates the need for trained personnel to execute the reconstitution procedure, ensures sterility up to the point of administration, and eliminates complex mixing and measuring to result in an accurate delivered dose volume.

Advanced design ergonomics of the delivery devices provide the capability to self administer, reducing the need and cost associated with a physician visit. All VersiDoser™ and VRx2™ intranasal delivery devices incorporate novel safety and ease-of-use features including the “Safety Interlock” which prevents inadvertent discharge of the device dur-



Figure 6: VRx2™ blister for reconstitution.

ing handling and secures the device from being repurposed or abused after it has been used. The user provides the force required to actuate mechanically operated mono- or bi-dose intranasal delivery systems.

Variability in the user hand strengths and actuation speeds can adversely influence spray characteristics of mechanically operated intranasal delivery systems, resulting in inconsistent delivered dose volume or spray-plume characteristics such as particle size or particle distribution, that are critical to optimum deposition and uptake within the nasal cavity. These dispensers employ a threshold-force actuation mechanism that requires a minimum force be exerted by the user before the delivery system will operate. The threshold force can be calibrated to ensure it can be used by a broad range of users. This feature reduces the influence of the user on the dispensing process and results in a consistent, reliable delivered dose volume, spray size and geometry.

The VRx2™ dry-powder delivery systems self pressurises at the time of administration and provides for direct delivery of the drug or biologic as a dry powder systemically or locally via the nasal route (see again Figure 4).

PLATFORM PERFORMANCE OVERVIEW

The MVP™ unit-dose rapid form-fill-seal manufacturing process demonstrated that for a 125 µL target fill, fill repeatability was tightly controlled within $\pm < 1.0$ µL. Figures 9 and 10 summarise the performance test results of delivered dose consistency and delivery efficiencies for a 100 µL liquid mono-dose nasal delivery system. Dose delivered volume exceeded 105µL with a high degree of consistency ($\sigma=4.8$ µL) for a

dose efficiency approaching 85% of fill volume actually delivered.

Droplet size distributions measured at two distances indicate an overall D50 median size of 65 µm (range 30-114 µm) at 35 mm and 92 µm (range 46-197 µm) at 65 mm. The span at both distances was approximately 2.3. The percentage of droplets < 10 µm was 4.3% (range 0-8.3%) and 1.9% (range 0-3.2%) at 35 and 65 mm, respectively.

The above data are representative; each performance characteristic – delivered volume and mean droplet size, for example – is readily customisable via appropriate modification of blister geometry and various piercing nozzle dimensions.

CONCLUSION

Exigencies related to the need for improved systemic administration have propelled the nasal cavity and capillaries to the forefront of preferred routes for delivery of drugs and biologics. Logistical issues of storage, ease of use and rapid deployment, especially in relation to vaccines and CBRN countermeasures, demand a quantum leap in our present ability to manufacture, store, and rapidly deploy unit doses of critical medicines that are readily accessible and simple to administer. Mystic Pharmaceuticals



Figure 7: Mystic VersiDoser™ unit-dose Blister with VJet™.

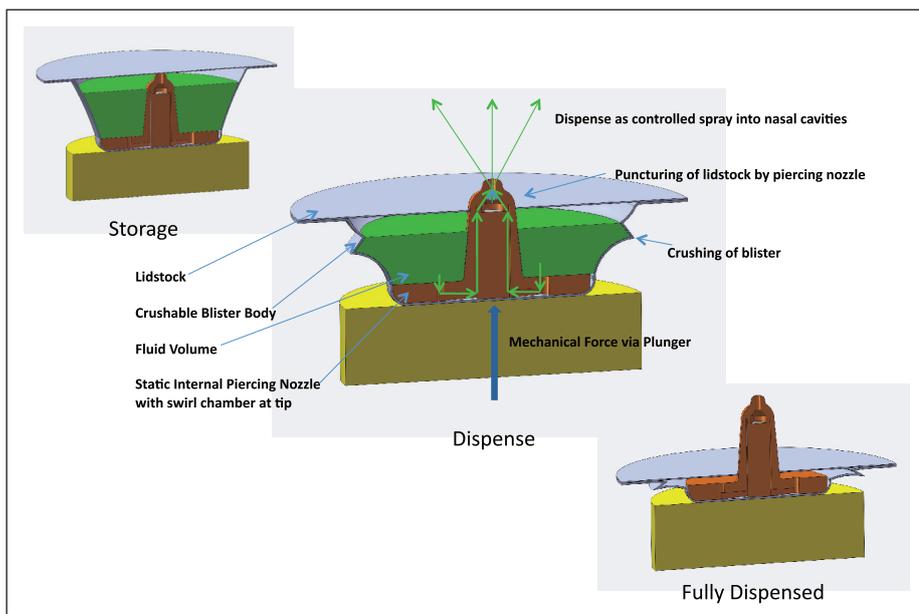


Figure 8: Versidoser™ unit-dose blister dispense sequence.

has developed a platform nasal delivery technology that addresses each of the present pitfalls in the current production to administration chain from packaging to final use and disposal.

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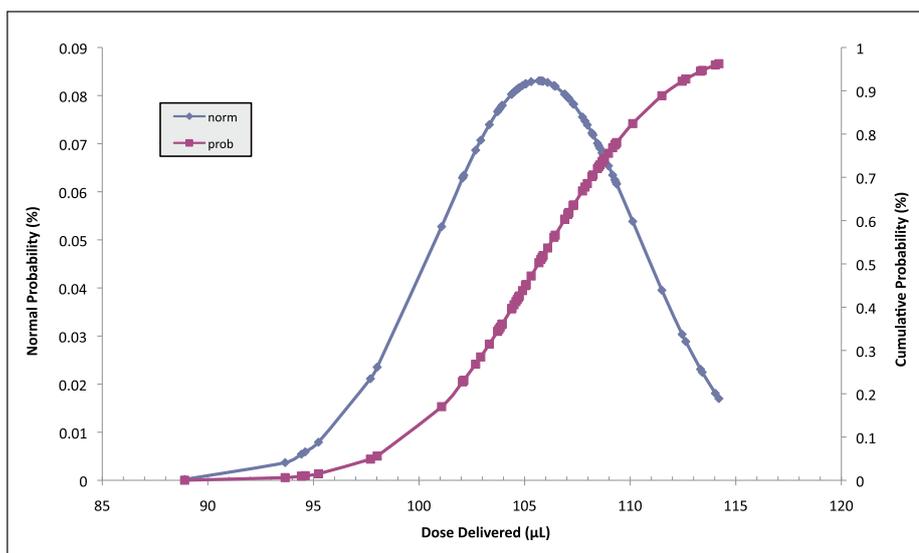


Figure 9: Versidoser™ nasal (as liquid) dispense efficiency.

n	70
Mean	105.65 µL
Median	105.99 µL
Eff(%)	84.52
stdev	4.80
min	88.90 µL
max	114.2 µL

Figure 10: Dose summary.

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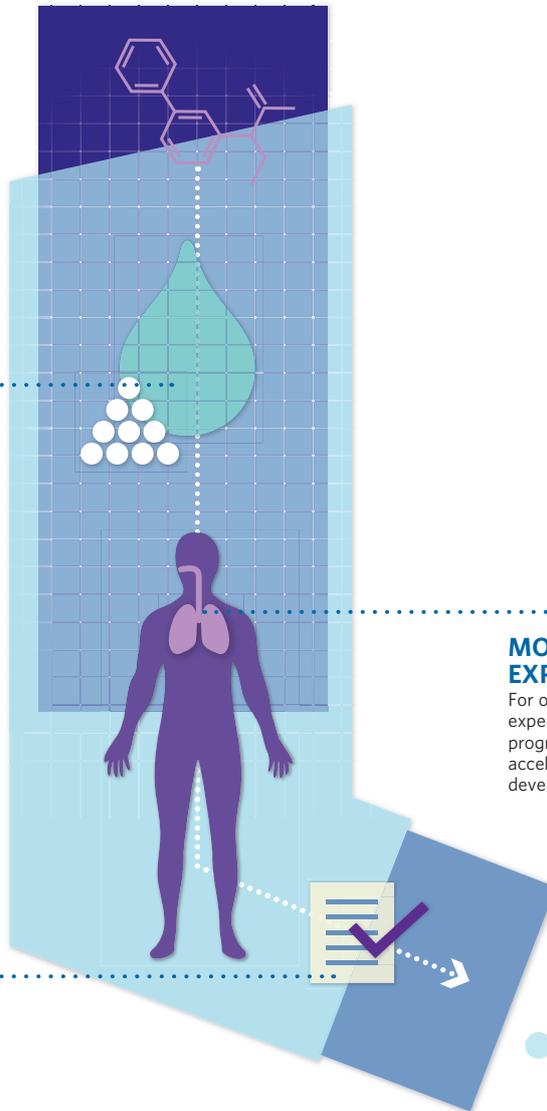
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