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This edition is one in the series of ONdrugDelivery publications. Each issue focuses on a specific topic within the field of drug delivery, and is supported by industry leaders in that field.

Full contact information appears alongside each article. Contributing companies would be delighted to hear from interested readers directly. ONdrugDelivery would also be very pleased to pass on to authors, or answer as appropriate, any queries you might have in relation to this publication or others in the series.

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DDL21
drug delivery to the lungs 21

Drug Delivery to the Lungs 21

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INGREDIENT-SPECIFIC PARTICLE SIZING:

REDUCING RISK, CUTTING COST AND SAVING TIME IN PRECLINICAL INHALABLE FORMULATION DEVELOPMENT

In today's fast-growing inhalables market, the availability of suitable, efficient and cost-effective means of gathering particle analysis data for pulmonary formulation is clear. In this article, Dr Oksana Olkhovyk, Senior Scientist, and Linda Batykefer, Marketing Manager, both of ChemImage Corporation, provide the latest about cutting-edge imaging tools for ingredient-specific particle sizing that ChemImage is putting at the disposal of the global pharmaceutical industry.

INTRODUCTION

There is an abundance of evidence supporting the fact that the markets both for respiratory drugs and respiratory drug delivery technologies are healthy, vibrant and growing. In recent years, whilst pharmaceutical company product pipelines overall have been reduced, along with the number of new drug approval applications submitted to regulatory authorities, pharmaceutical companies are continuing to pursue new delivery methods for their drug products. The inhalation and nasal products had combined sales exceeding US$22 billion in 2007 for treatment of asthma, COPD, allergic rhinitis, influenza, migraine and osteoporosis, and for use in general anaesthesia. [1]

One common trend is to develop respiratory delivery technologies for drugs currently administered via injection. Despite some initial problems, such as the failure of Pfizer's Exubera (inhaled insulin), the concept of systemic delivery via the lung is by no means dead, and many companies continue to develop inhaled drug products.[2]

While the indications for many inhalable and nasal drug delivery products have been somewhat limited to diseases such as allergic rhinitis and asthma, this is likely to change soon. Continuous research and development activities are gradually opening up opportunities in new therapeutic areas.

> "A MATERIAL ADVANCE IN THE SPEED, COST AND LEVEL OF DETAIL AT WHICH COMPANIES DEVELOPING INHALABLE FORMULATIONS CAN INVESTIGATE THEIR PRODUCTS' PROPERTIES AND BEHAVIOUR".

Nasal drug delivery is becoming more common due to the potential for increased drug uptake rates, improved bioavailability for certain drugs (relative to oral dosing), and convenient administration. A growing number of nasally delivered, systemically acting drugs for a number of therapeutic areas are reaching the market or are in the pipeline.[3]

Other areas where new nasal and inhalation drug delivery approaches could provide an alternative to current dosage forms (such as intravenous administration) are crisis situations (seizure and heart attack), motion sickness and psychotropic drugs.[3]

WHY PARTICLE SIZE MATTERS

For nasal sprays and aerosolised products, there are two important measures of particle

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size. The first measurement is that of the aerodynamic particle size, which is traditionally measured via cascade impaction, and is the key method of predicting where particles will deposit in the nose, oesophagus or lungs.

The second measure, the drug particle size, is an important determinant of the rate of dissolution and availability to sites of action within the nose (optimally approximately 10µm) or the lungs (<5µm). Therefore drug, or drug aggregate, particle size distribution (PSD) should be characterised in the formulation both within the primary container and within the aerosolised droplets.[4]

INGREDIENT-SPECIFIC PARTICLE SIZING

The ability to gather general, basic information for a given formulation about aerodynamic particle size and particle size distribution is of course an essential starting point in successful product development. However, traditional methods only provide the most rudimentary, purely physical data and cannot differentiate as to what a given particle comprises chemically.

There is so much more useful information to unlock. In reality, inhaled formulations are rarely, if ever, comprised of just one ingredient. There will usually be at least two components; the active pharmaceutical ingredient (API) and an excipient. Furthermore, the presence of more than two ingredients is becoming more commonplace as combination products – containing two APIs plus an excipient – are developed.

It cannot be assumed that all ingredients have similar physical characteristics, exhibit uniform particle size distribution nor that they behave in the same way. Thus, information pertaining to the particle size of specific ingredients represents a significant advancement and holds many advantages.

Ingredient-specific particle sizing (ISPS) is the technique offered by ChemImage which fulfils precisely this requirement for particle size data.

The technique uses ChemImage's unique technology combination of Raman chemical imaging, optical microscopy, and automated data gathering software to identify particles based on a unique chemistry (for example API versus excipient) and physical size information. Chemical information is based on the component chemistry identified by the unique Raman scattering.

An example of ingredient-specific particle size distribution data for a sample formulation containing two APIs is shown in figure 1. The

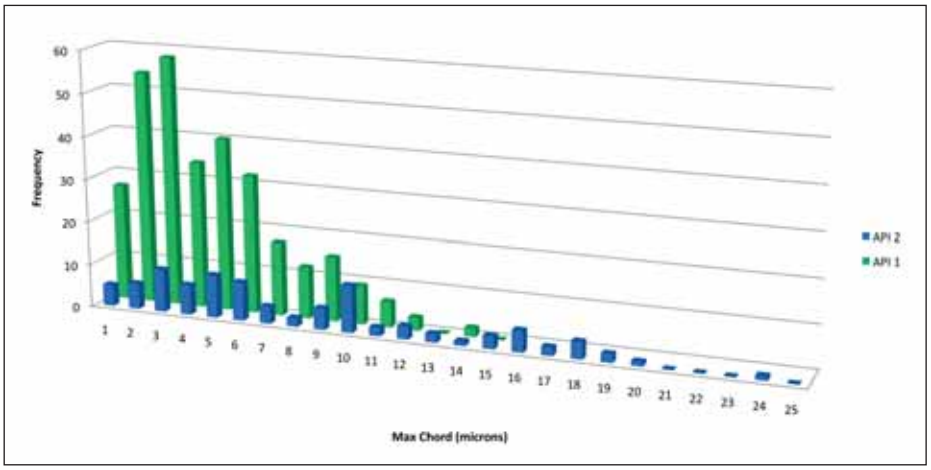

Figure 1: Example particle size distribution (PSD) chart showing ingredient-specific PSD of two APIs.

data is obtained from the combined information of the optical and Raman chemical image.

See boxed text on page 8 for more information on Raman chemical imaging and Raman spectroscopy.

Raman spectroscopy is a very selective vibrational technique and is often used in the pharmaceutical industry to identify drug polymorphs (different crystalline structures that are made of the same molecules, but exhibit various crystal habits or packing). With the ability to detect such small spectral differences, Raman spectroscopy is very comfortably able to differentiate between various materials in a pharmaceutical formulation, including the drug substance and various excipients (see figure 2).

Ingredient-specific particle sizing is especially useful for drug-specific particle sizing of both metered dose inhalers (MDIs) and nasal spray suspensions. The method was initially investigated in collaboration with the US FDA to achieve drug particle size distribution measurements for nasal spray suspensions.[5] In addition to investigating formulations for API particle size distribution, ISPS has been found to be useful for the study of drug/drug and drug/excipient aggregates.

Particle size is directly related to deposition location in the body as well as bioavailability. Aggregates, which in effect bring about an increase in overall particle size, cause a number of problems including:

- clogging of the medical device
- deposition in the wrong or unwanted part of the body
- changes in bioavailability

Readily available, high quality drug particle size data could provide the necessary information for conclusive in vitro bioequivalence (BE) comparisons of drug PSD, including PSD of dispersed and agglomerated API particles, as well as the extent of agglomeration in the product.[5]

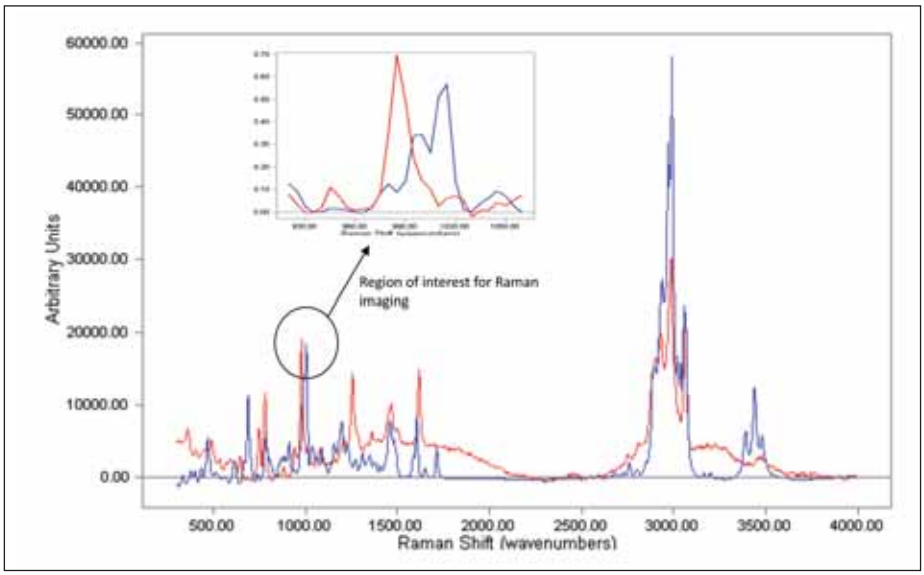

Figure 2: Raman Spectra of API components showing the ability of the Raman method to be used to distinguish the two API materials from one another.

Obtaining drug particle size information is important from a cost perspective. Prior to entering clinical trials, this additional information can prove to be valuable, raising confidence and lowering risk of failure for *in vivo* biostudies.

The value and importance of gaining this information before taking the expensive step of beginning clinical trials cannot be emphasised enough.

To give another example, in generic product development, if drug PSD of the generic is found to be not equivalent to (or outside of acceptable variability thresholds of) the innovative product's PSD, clinical trials can be postponed until the acceptable drug PSD is reached – saving significant time and money for generic companies.

Ingredient-specific particle sizing technology and service helps innovative drug developers to characterise and design their formulations better and, further on in development, as part of batch release testing.

With the increase in interest from innovative drug developers in inhalation and nasal drug delivery, methods that characterise formulations without destroying the sample are increasingly needed.

With additional information related to drug particle size and material composition at their disposal – information which was not easily accessible in the past – innovators are even better equipped to design unique, hard-to-duplicate formulations.

ISPS has proven especially useful for innovative drug developers who are interested in combining multiple drug substances in one formulation. While cascade impaction is useful for MDIs and DPIs when only one active ingredient is present, the situation becomes more complicated when two APIs are present. Raman chemical imaging has been evaluated as a possible candidate to replace cascade impaction as a tool to determine chemical identity PSD. An example of such an application of ISPS technology follows.

RAMAN CHEMICAL IMAGING FOR PSD OF TWO APIS IN COMBIVENT™ MDI

The MDI is the most common device for therapeutic aerosol delivery, second only to tablets among self-medicated dosage forms.[6] The PSD of the drug substance in the aerosol plume is a very important parameter and, in regulatory terms, is a required measurement for *in vitro* testing of MDIs.[6] A typical MDI formulation contains API, propellants and surfactants. Although PSD of the drug can be easily determined prior to the formulation, it is a challenge to establish it in the finished product.

The standard traditional apparatus for the *in vitro* determination of PSD information is the Anderson cascade impactor (ACI). A complete ACI analysis includes introduction of the sample into the ACI where particles are separated on the basis of their aerodynamic size, this is followed by extraction of the drug substances from the ACI plates, final filter, USP throat and mouthpiece adaptor, and finally performing quantitative chemical analysis by either HPLC or spectroscopy methods.

The procedure is time consuming, labour intensive and destructive. Presence of non-volatile excipients in the formulation or a second API may complicate particle size characterisation even further. Analysis of the deposition profiles may indicate formulation issues such as agglomeration of APIs or physicochemical stability (polymorphism, hydration) after actuation. Furthermore, a large variability in results has been observed between different operators and different ACI units. As a consequence, there is a high demand for the replacement of the ACI with an alternative technique capable of concurrently performing PSD determination and chemical identification. [6]

In a previous study, Raman chemical imaging (RCI) was evaluated as a method for identifying two API species on cascade impaction plates and characterising drug interaction in Combivent® Inhalation Aerosol (Boehringer Ingelheim Pharmaceuticals Inc, Ridgefield, CT, United States), an MDI sample containing two APIs. RCI successfully identified each API particle and the total number of particles and PSD for each API and PSD of aggregated API particles were reported. [6]

ChemImage had successfully applied RCI to measure ingredient-specific size distribution in formulated nasal sprays and aerosols. This investigation was initially reported in 2005; significant progress has been made since to optimise the technique and enhance the capabilities of RCI for the pharmaceutical industry. Issues have been addressed related to automation, image processing, and particle size analysis by applying an automated method of data collection and analysis of fused RCI and brightfield imaging.[7,8] A new, patent-pending image processing method has been developed to evaluate each particle in the field of view individually, rather than collectively.[9]

Using this image processing technique, the original Combivent RCI data reported by Guo *et*

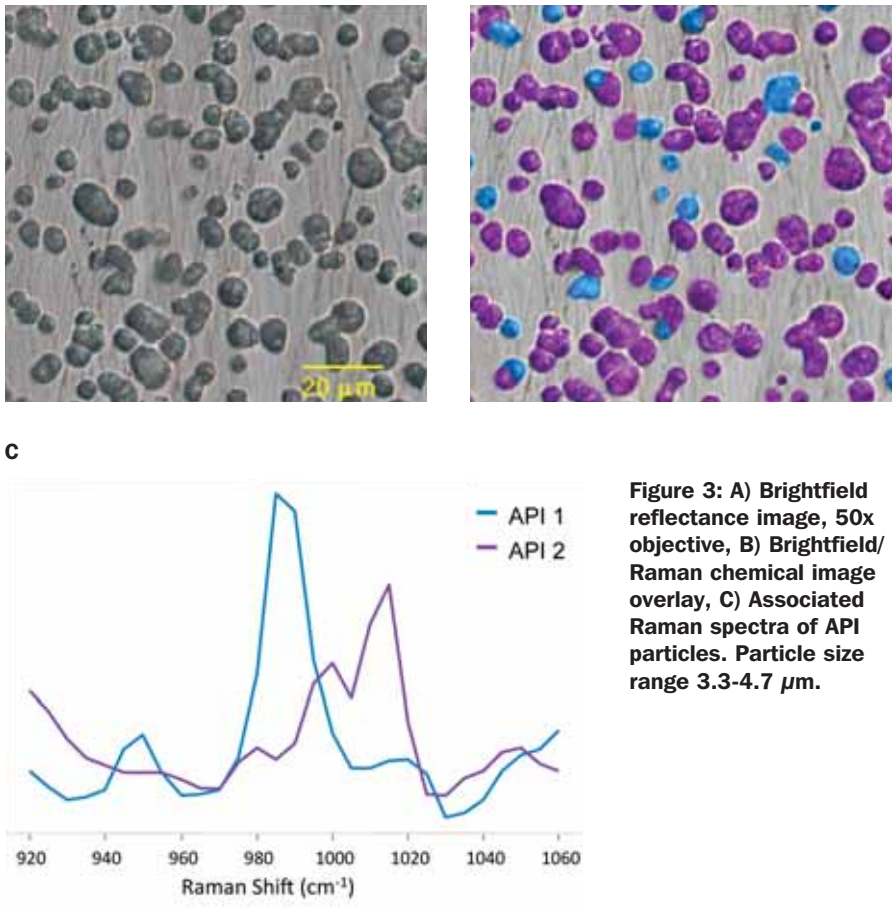

Figure 3: A) Brightfield reflectance image, 50x objective, B) Brightfield/ Raman chemical image overlay, C) Associated Raman spectra of API particles. Particle size range 3.3-4.7 µm.

al was revisited. API 1 (albuterol sulfate) and API 2 (ipratropium bromide) are presented as purple and blue in the brightfield / Raman binary image overlay (figure 3). Intensity maps were developed for each API using an iterative threshold process. Once the particle map is produced, a feedback loop is initiated which confirms the chemical identity against the Raman spectrum and validates the particle size against the brightfield optical image. This individual particle identification approach allows for a more accurate and reliable drug PSD measurement, effectively addressing concerns of accurate size measurements in the previous publications.[5] This combined image analysis approach helps to avoid the issue of over- or under-sizing particles due to Raman signal intensity – which is related to size of the particle.

CHEMIMAGE'S SERVICES: HOW AND WHEN?

The ISPS services offered by ChemImage and described here represent a material advance in the speed, cost and level of detail at which companies developing inhalable formulations can investigate their products' properties and behaviour.

The major advantage of utilising these contract services is the ability to understand the drug properties within the formulation. RCI provides drug particle sizing and distribution information and also provides information about aggregates. What is the drug PDS for each API? What particles are aggregating? Are drug particles aggregating or are drug and excipient particles aggregating to one another? Is this related to the device delivery or does this happen in the bulk formulation?

ISPS can be used during product development, specifically formulation development, as well as R&D for novel or existing formulations and during manufacturing for batch release testing. Possessing this information could ultimately result in, for example, faster ANDA filing, or more efficient and successful clinical trials. With a better understanding of the formulation, companies can mitigate risk in a number of steps during development for approval.

The earlier in formulation development this technique is employed, the better the chances of identifying incorrect drug particle size distribution, or aggregation issues.

If being used as part of a BE study, this method can also be used to gain an understanding of the innovator drug product. This testing can be done early on before the innovator or generic product is even in development, or it can be done in parallel.

TO OUTSOURCE RESEARCH OR PURCHASE EQUIPMENT?

ChemImage typically offers its ISPS services on a contract research basis. However, it is also possible to purchase the equipment necessary to do this work from ChemImage. This is especially useful for organisations which plan to do a significant amount of drug PSD testing in the future. Larger volumes of sample testing may make purchase of the equipment more cost effective. Purchase of the equipment is a capital expense, but also offers customised options for multiple imaging platforms including microscopic Raman and Near-IR or Fluorescence chemical imaging capabilities in addition to basic optical microscopy and Raman spectroscopy.

ABOUT CHEMIMAGE:

Founded in 1994 and headquartered in Pittsburgh, PA, US, ChemImage provides revolutionary Raman, Near-Infrared and Fluorescence chemical imaging technologies for chemical and biological applications in numerous global industries including

Q: What is Raman Chemical Imaging?

A: Raman chemical imaging builds on the ability of spectroscopy by adding a spatial context to the chemical information provided. Raman Chemical Imaging (RCI), a method that combines the capabilities of molecular spectroscopy and advanced digital imaging, details material morphology and composition with a high degree of specificity in a non-contact, non-destructive manner.

A Raman chemical image provides a Raman spectrum at each pixel in the image, providing spatially resolved Raman spectroscopic information. Interrogation of individual pixels assists in the interpretation of the data. Presence or absence of API within a field of view is determined by whether or not the Raman spectral features characteristic of the drug are present. Imaging allows one to understand size, shape, and spatial distribution of chemical components which provides a number of advantages of simple Raman spectroscopy, and in particular drug particle sizing for nasal and pulmonary drug products.

In the wide-field RCI approach, digital images are acquired at pre-defined Raman spectral regions, by imaging an area through an electro-optically controlled, liquid crystal tunable filter (LCTF) which serves as an imaging spectrometer. The RCI microscope simultaneously provides diffraction-limited spatial resolution (approaching 350 nm for high signal-to-noise images) and high Raman spectral resolution. The no-moving-parts approach employed to construct Raman chemical images enables fusion of optical and Raman chemical imaging data. Fused optical/Raman images are used to guide the size measurements, differentiation between drug aggregates and individual particles. This approach helps eliminate problems often seen with morphologically-directed, confocal Raman spectroscopy, which requires precise, repeatable stage translation.

Q: What is Raman spectroscopy?

A: This is a spectroscopic technique used to study vibrational, rotational, and other low-frequency modes in a sample system. It relies on inelastic scattering, or Raman scattering, of monochromatic light, usually from a laser in the visible, near infrared, or near ultraviolet range. The laser light interacts with phonons or other excitations in the sample system, resulting in the energy of the laser photons being shifted up or down in energy. The shift in energy gives information about the phonon modes in the system.

Scattered photons from the illuminated sample spot are collected with a lens and sent through a monochromator – or in the case of imaging an imaging spectrometer. Wavelengths close to the laser line, due to elastic Rayleigh scattering, are filtered out while the rest of the collected light is dispersed onto a detector.

pharmaceutical, anatomic pathology, forensics and threat detection.

The ChemImage workforce of researchers, software designers, hardware developers, scientists, business analysts and administrative support has tripled in the new Millennium, as more and more industries begin to understand and integrate the power of chemical imaging as a tool for realising their vision.

ChemImage currently has an extensive patent portfolio including 75 issued US patents, 12 allowed patents and has over 100 US and foreign patents for technology and methodology advancements across all of our lines of business.

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COMPANY PROFILE – COSTER PHARMA

Coster is a leading provider of both aerosol components and filling machines for the pharmaceutical, personal care and cosmetics industries. Founded in the early 1960s, now with an annual turnover of €150 million, Coster has more than 40 years' experience in the design and manufacture of high-quality packaging systems.

Coster is the sole company worldwide supplying integrated aerosol and spray solutions, including:

- MDI valves and inhalers for HFA and CFC
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- Filling lines for inhaled, nasal, oral, and topical products

Coster's robust and reliable technology allows it to meet the pharmaceutical industry's stringent quality standards and product safety features, while maintaining competitive prices.

Coster's R&D Centre offers formulation and re-formulation services for selected aerosol and spray OTC products. Customised aerosol courses can be hosted in-house or on-site.

COSTER PHARMA PRODUCT RANGE

Coster's range includes the following products:

- MDI valves: for HFA and CFC
- MDI asthma inhalers: for HFA and CFC
- Salus nasal actuator: for sea-water solutions
- Nasal actuators & spray pumps: for different nasal applications
- Bag-On-Valves (BOV): for liquids, gels and viscous products

COSTER PHARMA

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Production takes place in accordance with ISO 15378:2006, an international certification which encompasses ISO 9001 procedures and cGMP guidelines applied to Primary Packaging Materials for Medicinal Products.

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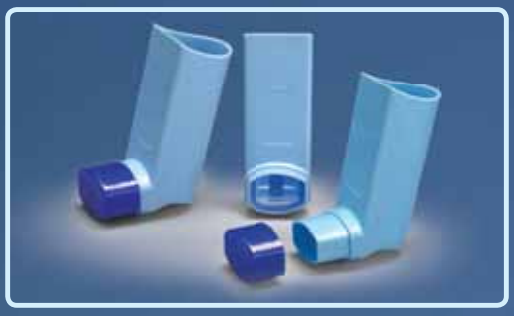

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OPTIMISING DRUG AND DEVICE TOGETHER FOR NOVEL AEROSOL THERAPIES

In certain inhalable product delivery applications, the use of a nebuliser can bring benefits compared with using MDIs or DPIs. In this article, Dr Manfred Keller, Executive Vice-President and CSO of PARI Pharma, and Dr Martin Knoch, President, outline the case for nebuliser use and provide examples of how PARI Pharma has developed tailored versions of its nebuliser technology platform, eFlow®, in parallel with different pharmaceutical products, for use by various patient groups and in the treatment of a number of diseases.

ADVANTAGES OF NEBULISED DRUG THERAPY

When treating various respiratory diseases, inhalation of aerosols to the lungs is the preferred route of administration of pharmaceutical compounds. Unlike pressurised metered dose inhalers (pMDIs) and multidose dry powder inhalers (DPIs), nebulisers can be used across a wide dose range (μg- up to gram-range) without loss of overall delivery performance. Unlike single-breath administration with pMDIs and DPIs, patients take treatment during multiple consecutive spontaneous breathing manoeuvres. Further, the treatment requires only minimal coordination and effort in comparison with pMDIs or DPIs.

Patients with severe disease who experience impaired breathing and co-ordination capabilities can master the use of a nebuliser. Various drug compounds can be nebulised, including peptides (e.g. Colistin), proteins (e.g. alpha-1 antitrypsin), or antibiotics (e.g. tobramycin), and drugs with poor lung tissue penetration (Ciclosporin A). Compared with individual actuations from a pMDI or DPI, nebulisers generate a large amount of fine aerosol which enables the drug to be more evenly distributed to the large surface area of the lungs (best illustrated by "wetting" a tennis court area).

Nebulisers are particularly useful for those drugs which require high dose deposition to the lungs, or for distinct patient populations, such as those with severe disease, young children, the elderly, or mechanically-ventilated patients in a hospital intensive care unit.

While nebulised drugs receive marketing authorisation from the US FDA or European agency (EMA) via a separate new drug application (NDA), nebulisers receive market clearance in the US via a 510(k) premarket notification (CDRH Guideline 784), and by CE marking in the EU. The nebuliser regulatory pathway is advantageous, since inhaled liquid formulations can be tested and clinically evaluated faster and more economically than pMDIs and DPIs. Regulatory approval is usually less burdensome and costly.

ADDRESSING UNMET NEEDS WITH AN ADVANCED AEROSOL PLATFORM: EFLOW®

Looking ahead, the acceptance of nebulisers in a competitive market will require development of improved devices which meet patients' and caregivers' needs. Special consideration to superior delivery efficiency with consistent droplet size distribution and dosing during treatment is essential along with treatment times significantly reduced compared with current approved nebuliser therapies. Further, nebuliser features that address ease of use, small size, portability, silent operation, and simple cleaning will help improve patient acceptance to nebuliser therapy.

With the objective of fulfilling these requirements, PARI Pharma developed the eFlow® device platform which utilises a perforated, vibrating membrane technology to generate liquid aerosols of distinct droplet sizes. The eFlow device platform has a significantly higher delivery efficiency than established jet, ultrasonic, or general purpose vibrating-mesh nebuliser systems used with current approved nebulised drug products. The higher delivery efficiency allows for dramatically shorter inhalation times and a substantial reduction of drug volume and

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PARI PHARMA`S ADVANCED DELIVERY PLATFORMS

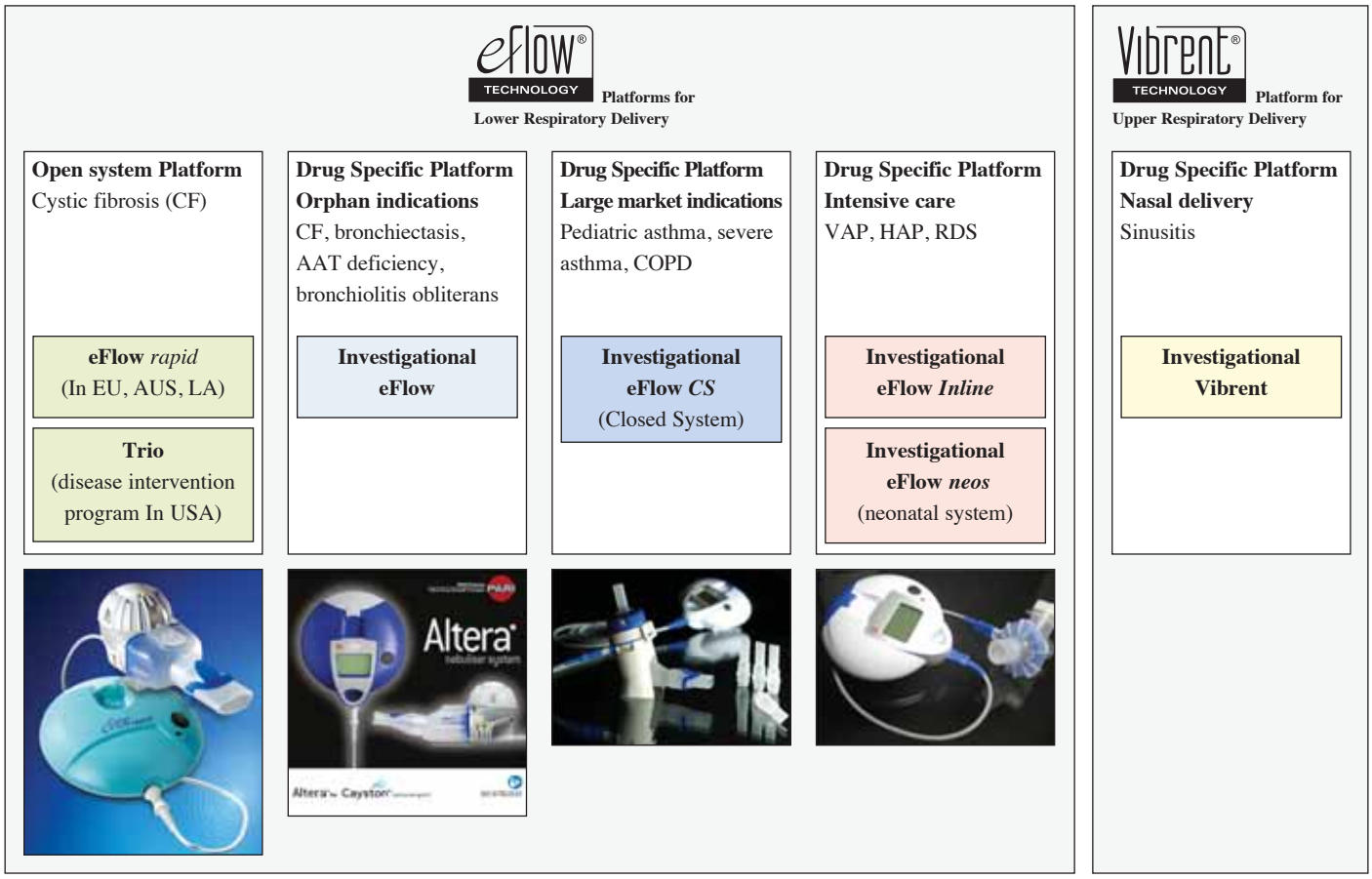

Figure 1: eFlow® Technology platforms: lower respiratory system delivery (eFlow®) and upper respiratory system delivery (Vibrent®)

dose, as higher drug concentrations are feasible and less drug is wasted.

Where the approved nebulised drugs of today focus on volume fills of 2-5 ml (7 min up to 30 min range), the targeted formulations of the future in eFlow Technology devices will be in the 0.5-2 ml range (2 min up to 4 min) which encourage improved patient adherence. This feature, qualifies eFlow Technology devices for the delivery of expensive drugs and in situations when long treatment times would be a strong deterrent to patient compliance.

Based on numerous studies and initial market experience, eFlow Technology has proven to be robust and suitable for nebulisation of many drug products including fragile molecules such as rhDnase (Pulmozyme®), alpha-1 antitrypsin, siRNA, DNAzyme, as well as novel liposomal drug formulations.[1]

VERSATILITY FOR CUSTOMISED CONFIGURATIONS

eFlow Technology devices are able to deliver a wide range of drug volumes (0.5-8 ml) and dosages (0.01-1000 mg) and have been customised to meet with dedicated applications and patient requirements.[2] eFlow Technology is attractive for many new and proven drugs as the drug and device are developed and optimised together and approved via mutually conforming labels. Further, eFlow Technology is versatile with respect to target droplet size (mass median diameter (MMD) 2.5 μm up to 5.0 μm) and offers customisation options for lower (lung) and upper (sinus) respiratory drug delivery. eFlow Technology devices are intended for home use as well as the hospital setting, including critical care settings, and are designed as a hand-held version, or as a stationary configuration for use with ventilators (see figure 1). Certain eFlow Technology devices can incorporate an electronic treatment monitoring function to measure compliance.

PROVEN TECHNOLOGY WITH EXCEPTIONAL PATIENT ACCEPTANCE

An eFlow Technology device called eFlow® *rapid* was designed to deliver comparable doses of currently available nebulised drugs used by cystic fibrosis (CF) patients and approved for use with jet nebulisers, such as the PARI LC PLUS. Since its launch in Europe in 2005, eFlow *rapid* has gained a market share of about 75% amongst European CF patients. The inhalation of TOBI® (tobramycin) with eFlow *rapid* has been shown to be safe and effective based on experience from daily practice and a clinical study demonstrating comparable tobramycin blood plasma levels and sputum concentrations.[3]

PIONEERING CHARACTERISATION OF NEBULISED DRUG PRODUCTS

Guidelines issued by the FDA and EMA on nasal and orally inhaled drug products contain testing specifications, but do not disclose how to carry out such tests. An assessment of nebuliser systems cannot be done with a simple gravimetric measurement, but requires the quantification of the drug content delivered under simulated breathing conditions.

The CEN nebuliser standard[4] describes a simplified type-testing method for the head-to-head comparison of nebuliser systems using an aqueous sodium fluoride surrogate solution. However, since physico-chemical properties of solutions and suspensions can deviate substantially from a sodium-fluoride solution, such results do not reflect specific drug/device interactions[5], especially when delivered using novel aerosol generation technology.

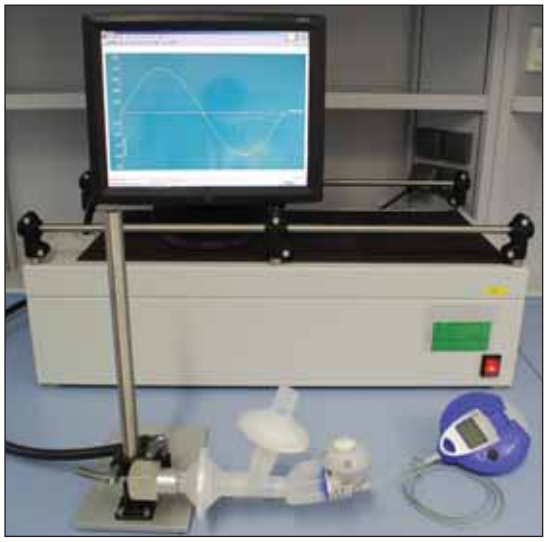

Figure 2: PARI Compas™ Breath Simulator test set-up

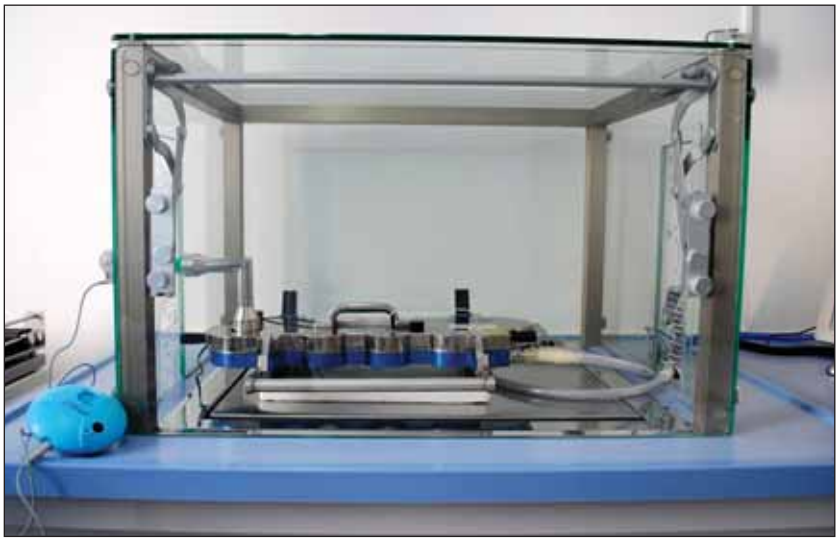

Figure 3: Climate box with New Generation Impactor (NGI) test set-up

Thus, the PARI Compas™ Breath Simulator (figure 2) is used for aerosol characterisation testing that allows measurement of the delivered dose of a nebuliser with breath simulation adjusted to realistic patient breathing conditions. The methods used for nebuliser testing (wet aerosols) are substantially different from those established for pMPIs and DPIs (dry aerosols). PARI Pharma was a key contributor to the development of these relevant testing standards which have been implemented for *in vitro* testing.

ACCURATE ASSESSMENT OF DROPLET SIZE

Measurement of nebuliser droplet size is typically conducted using two different methods: laser diffraction or cascade impaction with an Andersen cascade impactor (ACI) or the Next Generation Impactor (NGI). The latter is more suitable since its calibration at 15 l/min allows a more accurate measurement of nebulised aerosols.[6]

In order to avoid droplet evaporation and distortion of the size distribution, proper assessment of the droplet size requires cooling of the impactor for wet aerosols (nebulisers) to equilibrate the temperature of the emitted aerosol.[7] To this end, PARI Pharma developed a climate box allowing adjustment of the temperature of the cascade impactor as well as humidity and temperature of the air entrained into the nebuliser (see figure 3). This set-up allows for the investigation of various effects on the *in vitro* deposition performance of nebulised products, including effects caused by ambient humidity and temperature as observed with hygroscopic drug compounds.[8]

UNDERSTANDING DRUG AND DEVICE INTERACTIONS

Deposition of aerosolised drug into the lungs is determined by different factors, i.e. patient factors and drug/device factors. Individual lung anatomy and patient breathing manoeuvre have a major impact on drug deposition. In addition, the design, functionality and quality of the device and the interaction of drug formulation and device play an important role.

The droplet size can be heavily influenced by the viscosity and surface tension of the drug formulation. Hygroscopic drugs, such as di-sodium cromoglycate (DSCG) and colistimethate may absorb water from the ambient air causing particle growth within milliseconds. Thus, the fine particle dose (respirable particles < 5 μm) of a pMDI or DPI can be reduced significantly when hygroscopic drug is exposed to the humidity saturated human airways, while droplets generated by a nebuliser remain relatively stable.[8]

Adequate *in vitro* testing of a specific drug/device combination is critical to accurately characterising and identifying such complex interactions before proceeding into costly clinical trials.

FROM BENCH TO CLINIC: DSCG

In vitro assessment of various DSCG delivery systems, for the treatment of asthma, revealed extremely poor performance of Intal® pMDI and DPI systems, which led to the conclusion that inhaled DSCG may have been underrated in its therapeutic effect.[8]

We hypothesise that in order to achieve a remarkable therapeutic effect in the treatment of asthma, a much higher DSCG dose will be required at the target site, specifically to the mast cells located in the lung periphery. A clinical study was designed to prove this hypothesis comparing standard inhaled corticosteroid therapy with an isotonic DSCG solution administered via a small droplet eFlow Technology device in children above six months of age. Preliminary findings indicate that the DSCG administered via a small droplet generating investigational eFlow may be equally potent due to a higher and more distally deposited lung dose, compared with twice daily inhaled steroids as no therapeutic difference

	Lung deposition [mg]		Sputum concentration [mg/l]		C_{max} [mg/l]	
Product	TOBI	**Tobramycin PARI**	TOBI	**Tobramycin PARI**	TOBI	**Tobramycin PARI**
All patients	45.4	**46.0**	2.27	**2.59**	1.65	**1.29**
adults	46.8	**45.6**	2.65	**2.67**	1.81	**1.21**
children	44.1	**46.4**	1.99	**2.5**	1.52	**1.36**

Figure 4: Lung deposition of two 99mTC-DTPA labeled tobramycin solutions investigated in a crossover design study in CF patients (n = 16, 8 children, 8 adults) after inhalation of TOBI (300 mg/5 ml) via the PARI LC PLUS and Tobramycin PARI (150 mg/1.5 ml) via an investigational eFlow nebuliser.[11] Data on sputum concentration and C_{max} were obtained from a 28-day safety study in CF patients (n = 76, 38 children, 38 adults).[12]

could be observed after three and six months of treatment, respectively.[8]

MATCHING DRUG FORMULATION AND DEVICE: INHALED ANTIBIOTICS

Drug formulations and the delivery device can be mutually adapted and matched for optimal characteristics to reach the desired therapeutic target. Reformulation of known and proven compounds in a liquid format are commercially attractive as they present a relatively low development risk for potential drug product candidates and, thus, have become a preferred pathway for the development of new inhalation products.

The monobactam antibiotic Cayston® (aztreonam for inhalation solution 75mg) from Gilead Sciences was recently approved as a treatment to improve respiratory symptoms in cystic fibrosis (CF) patients with *Pseudomonas aeruginosa (P. aeruginosa)*.

PARI Pharma contributed pharmaceutical formulation development, analytics and aerosol characterisation to optimise the Cayston formulation with the device. The treatment time for this novel inhaled antibiotic therapy is 2-3 minutes compared with the current first-line therapy, which requires 15-20 minutes per dose.[10]

Another optimised drug/device combination currently in clinical development is a low-volume, high-concentration Tobramycin PARI inhalation solution (150 mg/1.5 ml) for nebulisation via an investigational eFlow nebuliser. The goal of this development was to decrease CF patient treatment burden by shortening the inhalation time to about one quarter, compared with TOBI (tobramycin 300 mg/5 ml) approved for delivery via the PARI LC PLUS jet nebuliser.

Data summarised from a gamma deposition and safety study (figure 4), demonstrated that nebulisation time could be reduced from approximately 16 minutes to four minutes with a similar deposited dose. Due to the higher delivery efficiency of the investigational eFlow device, only 150 mg (instead of 300 mg) of tobramycin was needed to obtain comparable lung deposition[11] and sputum concentration, based on data from a safety study conducted in 76 CF patients (38 adults and 38 children) over 28 days.[12]

The lower C_{max} indicates less drug was systemically absorbed which may reduce the potential for undesired ototoxic and nephrotoxic side effects. The shorter inhalation time could help to improve patient compliance and therapeutic efficacy from a long-term perspective.

DRUG PRODUCTS WITH UNIQUE PROPERTIES: INHALED LIPOSOMAL CYCLOSPORINE A

Over the past several years, PARI Pharma has developed a liposomal cyclosporine A (L-CsA) inhalation formulation as its lead proprietary drug product candidate. The formulation consists of unilammelar liposomes, equal to or less than 100 nm in size, that demonstrated a very favourable lung tissue penetration as well as excellent mucosal tolerability in preclinical testing. L-CsA has undergone a successful Phase Ib lung deposition study[13] and is currently being investigated in a multicenter, randomised, double-blind, placebo-controlled Phase IIb study for the prevention of bronchiolitis obliterans in lung transplant recipients.

A UNIQUE CONCEPT FOR PRODUCT PROTECTION: EFLOW® CLOSED SYSTEM

Another major advantage of the eFlow Technology platform is the option to use a proprietary blow-fill-seal ampoule containing the ready to use liquid inhalation formulation. A nebuliser with an integrated single-dose ampoule may be ideal for specific indications where ease of handling

and protection against the use of unauthorised medications are key factors to the regulatory pathway. In addition, this patented ampoule design allows the prevention of generic alternatives even after the original drug patents expire.

The eFlow closed system highlights three unique design features:

(1) A single dose ampoule that becomes an integral part of the device
(2) the ampoule is required to operate the device
(3) the ampoule is automatically opened when locked into the device.[14]

Thus, a customisation of nebulised drug therapy regarding age or disease or application-specific requirements can be adequately addressed.

DRUG DELIVERY IN A VENTILATOR CIRCUIT: EFLOW® INLINE

Aerosol delivery to mechanically ventilated patients is associated with high drug losses, poorly reproducible delivered doses (DD) to the patient, and rather low delivery efficiency (7.7% mean DD at the end of the endotracheal tube). PARI Pharma has developed a nebuliser configuration with an improved performance for ventilator use characterised by a high dose consistency independent of different ventilators and ventilation parameters.[15] This new eFlow *Inline* device may serve to improve the treatment of ventilator associated pneumonia (VAP) using, for example, nebulised antibiotics in critical-care settings.

A NOVEL UPPER RESPIRATORY DRUG DELIVERY CONCEPT: VIBRENT®

The Vibrent was developed to offer a new treatment option for patients suffering from chronic rhino sinusitis (CRS) affecting about 5-10 % of the population worldwide. The Vibrent is a novel device using pulsating airflow and enabling nasal drug delivery to the osteomeatal area and the paranasal sinuses as revealed from a gamma deposition study in 16 volunteers. Of the emitted aerosol, 71.5 ± 13 % deposited in the nose and 7.1 ± 1.4 % of this amount was found in the sinuses.[16]

Compared with nasal sprays, nasal retention was prolonged by about four-fold with the Vibrent. Our data provide evidence that ventilation and topical drug delivery to the posterior nose and osteomeatal area, including paranasal sinuses, is possible with the Vibrent offering new therapeutic perspectives for CRS and CF sufferers.[16]

SUMMARY AND CONCLUSION

PARI Pharma has an outstanding track record and strong expertise in the development and manufacture of nebulisers including large-scale manufacturing. Substantial know-how in formulation development, analytics and aerosol characterisation, all in compliance with GMP requirements and accompanied by a state-of-the-art QA, address all needs for the successful approval of nebulised drug products.

Development partnerships with small and large pharma companies, and the recent approvals of Cayston in the eFlow Technology device, Altera®, demonstrate PARI Pharma's ability to provide the full spectrum of knowledge and networks, including clinical and regulatory support and services, required to transfer a project idea into a drug and device combination product.

PARI Pharma has several proprietary clinical development programs ongoing either for licensing in later stages or marketing on its own.

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Plenary Sessions

The 2010 plenary sessions are scheduled Monday through Wednesday. Confirmed speakers are:

Mauro Ferrari, The University of Texas-Houston, U.S.A.
Nanotechnologies for Personalized Medicine

Raju Kucherlapati, Harvard University, U.S.A.
Genetics and Genomics in Clinical Medicine

Hiroshi Maeda, Sojo University, Japan
The Enhanced Permeability and Retention Effect in Cancer and Inflammation for More Selective Drug Delivery: Past, Present, and Future Outlook

Ramin Najafi, NovaBay Pharmaceuticals, U.S.A.
Creating and Growing an Innovative Company without VC Funding

Nicholas Peppas, The University of Texas-Austin, U.S.A.
Controlled Release 50 Years Later: Responsive Intelligence and Delivery by Design

Frank Szoka, University of California-San Francisco, U.S.A.
Role of Polymer Architecture in Tumor Drug Delivery

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InnovaSystems, Inc.
Technology Engineering

AUTOMATED ACTUATIONS FACILITATING COMPENDIAL TESTING OF NASAL SPRAY AND METERED DOSE INHALER PRODUCTS

For metered dose inhalers and nasal spray pumps, the testing of various product characteristics including plume geometry, spray pattern, dose-weight and dose content uniformity, is facilitated by automated actuators. In this article, Henrik G. Krarup, Vice-President, Business Development at InnovaSystems, Inc, describes how these actuators fit in at the heart of the product testing process and how this process is benefiting from innovative actuator designs.

The US FDA has formulated guidances for the pharmaceutical industry dealing with the various aspects of submitting data on NDAs and ANDAs for nasal aerosols, nasal sprays and metered dose inhalers (MDIs).[1-3] These drug delivery systems are designed for patients to administer by hand actuation and the guidance documents deal with the various characterisation aspects of the sprayed or aerosolised products.

For *in vitro* testing it is recommended to use automated actuations to minimise potential operator bias. For delivery systems that entirely rely on the force exerted by the human hand, the natural variation of the magnitude of this source of force has a direct bearing on the variability of droplet size distributions and spray patterns. Under these conditions automated actuations help to minimise the variability of data and thus facilitate product comparisons. Beyond pure statistical validation, automated actuators also save pharmaceutical employees long-term joint damage from repetitive movements during testing of these products.

ACTUATORS

Since 1989, InnovaSystems has developed automated actuators. From an engineering perspective the actuator converts one form of energy (compressed air or electricity) into mechanical force signified by movement of the actuator plate on which the drug delivery system rests. Previously, compressed air was considered an integral part of any lab environment, which was taken advantage of in the design of the early actuators. Control of compressed air has reached a mature state providing well functioning electronic valve components and pressure-resistant polymers for tubing.

To supply the necessary equivalent force of a strong human hand (around 80N) only 90 PSI (approximately 6kg/cm^2) is required from the compressed gas source. The actual amount of gas needed is small and many labs run their actuators from tanks enjoying the flexibility of switching between compressed air and nitrogen. This principle of operation provides a simple solution with a minimal amount of moving parts and need for maintenance.

The development of the pneumatic actuators has advanced from the stand-alone type NSP to the software controlled eNSP and the popular MightyRunt. All the pneumatic actuators (see figure 1) are controlled by specifying the amount of equivalent force that is needed for the actuation. During a time span of 10 years the actuators expanded their role and use from primarily delivering products for shot weights and dose content uniformity (DCU) to spray delivery for laser-based droplet size distribution determinations. As a consequence the MightyRunt actuator was designed with a low positioned actuator plate which allowed positioning of the nasal spray nozzle tip below the laser beam of the early laser diffraction instruments.

As laboratrory space became a priced commodity in pharmaceutical labs it often happened that the actuator would not have access to compressed air within its intended area of operation. Consequently a customer-driven need spurred the development of actuators operating on principles of electrical motors. However, this principle of operation is slightly more complicated than the pneumatic principle.

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Figure 1: Pneumatic Test Equipment

Electrical motors are well controlled but require an addition of threaded spindles or lead screws to provide translational motion. By observing Maxwell's modification of Faraday's law of induction (see figure 2) we can appreciate that by changing the magnetic flux, an electromotive force is induced. The electrical motor is thus realised by placing an electromagnet between two permanent magnets. When the electromagnet is charged by the electric source, the generated flux induces the electromotive force needed to turn the electromagnet around its axle, which becomes the rotor. The stationary part (in this case the permanent magnets) are referred to as the stator.

As mentioned above, a further addition of a lead screw, as used in the familiar micrometer caliper, will allow the transformation from rotational to translational motion. This has become the principle of operation of the electrical VA actuator (see figure 3), which is controlled by specifying the velocity required during the actuation.

InnovaSystems' dedication to providing superior automated test solutions has taken the electrical actuator to the next level – linear motor actuators.

Linear motors that originally were known from magnetic levitated train and plotter applications were previously highly priced, but have now matured to a lower price level such that they are serious competitors to traditional rotational motors. The primary motion of the linear motor is translational which for actuators offers a very desirable advantage over converting the movement of a rotational motor. By unfolding the stator of the rotational motor the induced force becomes linear rather than a torque (or rotation). Pulsing the electromagnets (see figure 4) allows the central coils to move in a highly controllable linear manner.

This operating principle by-passes the inherent friction-wear issue of the rotational motor such that the actuator in which it is used becomes more efficient, more accurate and less maintenance demanding. On the application side, the linear motor offers operation in either a force-based or velocity-based mode. This provides the advantage of reproducing performance of the earlier pneumatic and rotational-electrical actuators from one single actuator unit.

DETERMINING ACTUATION PARAMETERS

The FDA guidance documentation referred to previously recommends that the parameters chosen for the operation of the actuators should make the instruments perform the pump actuations in manners similar to those in which a trained patient would. To this purpose InnovaSystems has developed Hand Actuation Monitors (HAMs; see figure 5a) that allow operators to characterise hand actuations for determining the range of forces and velocities. Figure 5b shows results obtained from a HAM.[4] These devices significantly reduce the work associated with justifying the chosen actuator parameters.

COMPENDIAL TESTS

The actuator thus becomes the cornerstone of the test station that deals with the compendial test requirements for priming/re-priming, dose weight, content uniformity preparation, spray pattern and plume geometry. The stations are designed to be scalable to accommodate the different capacity needs from R&D to QC environments.

Single-product dose-weight testing may be performed on a Pump Actuation Weight Station (PAWS; see figure 6). As the pump is actuated the dose weight is automatically recorded in the software.

Multiple-product dose-weight testing may be performed on a NSP-DW or MDI-DW station. A gantry system sequentially moves 20 samples between the test rack and the actuator. Actuation and dose weight registration happens without any need for supervision. Waste material is handled through a vacuum system to a filter.

Preparation of samples for DCU may be added as a feature to the DW station (figure 7). A further gantry system now handles capped

$$|\mathcal{E}| = \left| \frac{d\Phi_B}{dt} \right|$$

where

$\mathcal{E}$ is the electromotive force

$d\Phi_B$ is the change in the magnetic flux

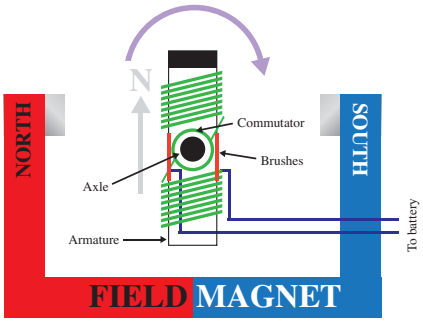

Figure 2: Maxwell's modification of Faraday's Law of Induction, and the principle of a rotational motor

Figure 3. The Velocity Controlled VA Actuator

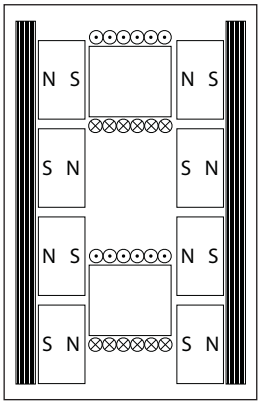

Figure 4: Configuration of a Linear Motor. Centre coils perform a linear upwards or downwards motion between electromagnets sequentially switched on and off

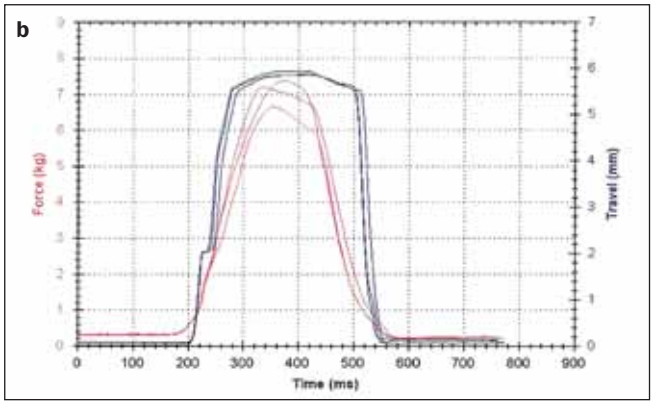

Figure 5: a) HAM with a load cell for electronic transfer of Hand Actuation Parameters to the actuator software. b) Travel and Force Curves obtained with the HAM Device

sample tubes and brings them to the actuator where the subsample is delivered to the test tube. A predetermined amount of solvent is added to the subsample, which subsequently is capped and agitated in its preparation for DCU. Weights are documented from every step and all data ported to an ASCII file which subsequently may be streamed to the customers LIMS system. The return on investment (ROI) is remarkably high if a complete stability study is considered, involving 10,000 tests including waste sprays, dose weights, DCU, multiple strengths, multiple lots and multiple pulls.

The pneumatic actuation principle is applied in the Fire Down 10 (FD-10) which allows simultaneous testing of 10 MDI canisters at a time. This performance specifically relates to "DCU Through Container Life". The canisters are first rotationally or vertically shaken, and then fired such that the canisters quickly and efficiently can be DCU tested at initial fill % and later at 50% full. The discharge is evacuated to a filter through a vacuum system. This is a compact stand-alone system with a keypad programming surface. The FD-10 instrument was displayed previously together with the other pneumatic systems in figure 1.

Plume geometry is not used in Quality Control (QC) for release but can be a useful tool during product characterisation of both NSPs and MDIs. Spray pattern however is used routinely in QC for release. Traditionally these tests have been performed with impaction systems such as TLC plates and fast-speed cameras. InnovaSystems has developed a non-impaction laser-based system that allows automated acquisition of digitised images of the spray pattern and plume geometry of both NSPs and MDIs (figure 8). The software allows the operator to specify an electronic shutter and threshold level such that the perimeter of the true shape of the spray pattern includes a high proportion (inclusion ratio > 95%) of the total pattern as recommended by the FDA.

SUMMARY

InnovaSystems has a long tradition of providing high-quality equipment for the testing of drug delivery systems. The company takes great pride in providing the most advanced and reliable actuators that form the core of its scalable test systems for priming/re-priming, dose weight, preparation for dose content uniformity, spray pattern and plume geometry.

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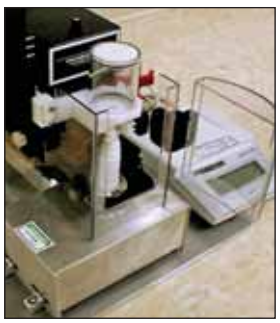

Figure 6: Pump Actuation Weight Station for automated dose weight determination of individual nasal spray pumps

Figure 7: Fully automated system for Nasal Spray Dose Weight determination. In addition, sub-samples are automatically prepared for Dose Content Uniformity testing

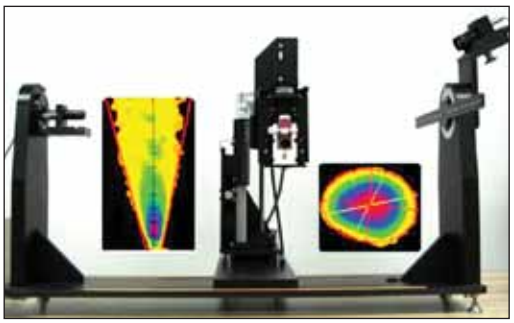

Figure 8: Aerosol Drug Spray Analyser for spray pattern and plume geometry of both MDIs (shown here) and nasal spray pumps. They colorized inserts show plume geometry (left) and spray pattern (right) images

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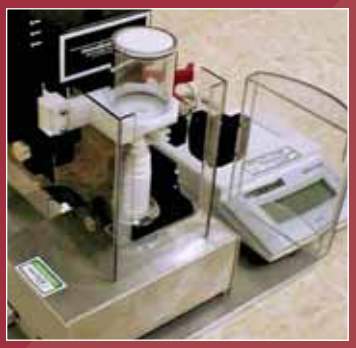

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ENVISION LASER-BASED IMAGING SYSTEM:

FULLY CHARACTERISES NASAL- AND DRY POWDER-BASED SYSTEMS

The *EnVision* system is a fast and effective platform for benchmarking devices to assess the impact of changes in design and how different ingredients are handled by different device platforms. It provides important insight into the fluidisation and behaviour of powder inside dry powder devices. Here, Dr Séamus Murphy, Manager, Imaging Division, and Dr Tim Stephens, Imaging Systems Engineer, both of Oxford Lasers, review current technology and application techniques and outline how advances in technology are utilised to characterise nasal sprays and dry-powder inhalers (DPIs).

Oxford Lasers has supplied groundbreaking imaging technology to the pharmaceutical and medical devices sector for over a decade, providing scientists and engineers with insight into device behaviour.

For nasal sprays the the Oxford Lasers *EnVision* system provides information on three areas of interest: the effect of changing operating conditions (for example, pump actuation force or velocity); how solution type affects performance; and the velocity profile across a typical nasal spray. We will also look at the complex flow inside the nasal cavity and how imaging techniques can assess the flow regimes through nasal passages.

For DPIs the *EnVision* system gives images of the fluidisation process and flow behaviour inside the device. Combined with advanced analytical techniques it is possible to collect information on the flow velocity, particle size and particle velocity.

EnVision systems (see figure 1) are designed to capture sequences of images from transient events. The unique platform employs a safety enclosure, short-pulsed laser light source, high-frequency camera and image analysis software to provide information on particle size, particle velocity, flow field vector analysis and general spray characterisation of spray pattern and plume geometry in line with US FDA guidelines. [1]

IMAGING HARDWARE

By courtesy of its Class I laser-safe enclosure system, the *EnVision* system conforms fully to all laser safety requirements. This means that the *EnVision* system can be positioned in any lab. At the heart of the system are a light source, high-speed camera and a suite of advanced software.

The light source is an Oxford Lasers *FireFly* pulsed diode laser system, designed for high-speed imaging applications. Operating at a wavelength of 808nm, the laser can provide very short pulses down to 500 nanoseconds in duration. Because the light source is pulsed, the captured images are free from motion blur and are suitable for use in more advanced analysis techniques. The laser can operate at up to 10,000Hz in continuous mode but for short periods can run in burst mode giving an equivalent frequency of 1,000,000Hz. The internally adjustable optics allow the user to configure the light source around different devices, and provide multiple modes of illumination[2] (for example, a light sheet for visualising a plane through a spray plume).

The high-frequency camera has a CMOS (complementary metal oxide semiconductor) sensor with large area pixels, giving optimum light sensitivity. The standard version can run at frame-rates from 500Hz to 10,000Hz at full resolution. Higher frequency options give a frequency range up to 1,250,000Hz with reduced resolution. These astonishing frame-rates mean that drug delivery processes can be viewed in unprecedented detail.

ANALYSIS TECHNIQUES

There are predominantly three types of image analysis used on nasal and DPI platforms, providing a range of data, for the evaluation of devices;

Figure 1: *EnVision* system with Class I laser safety enclosure

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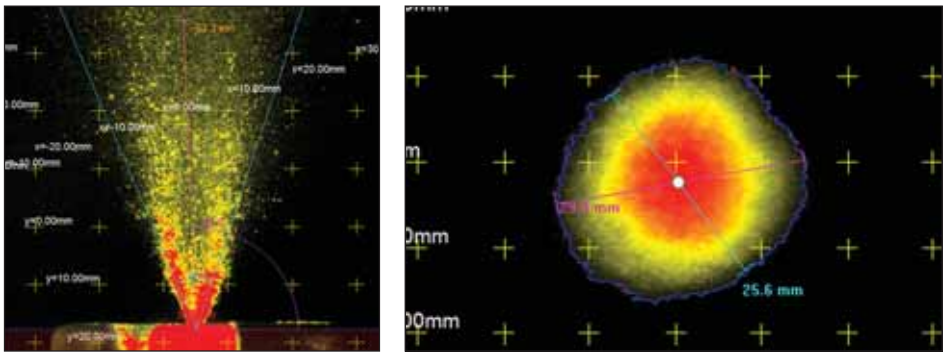

Figure 2: a) Plume geometry and b) spray pattern images from *EnVision* QC system with fully automated analysis

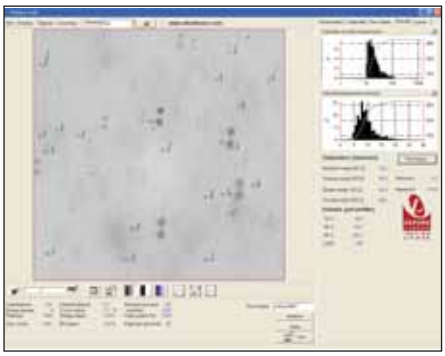

Figure 3: *VisiSizer* – particle size and particle velocity analysis for droplets in flight with background illumination. Particles appear black on a bright background

1. General Characterisation of plume geometry and spray pattern

This long-established technique uses a light sheet aligned either along the axis of the spray or orthogonal to it.[3] The Oxford Lasers *EnVision Patternate* software integrates a series of images of the spray, detects the boundary pattern or geometry and reports either spray pattern or plume geometry parameters. Figure 2 shows typical images of the spray pattern and plume geometry. This type of basic system is widely used in the pharmaceutical industry to test devices in accordance with FDA Guidlines. [1]

2. Particle Size Characterisation

Image-based particle sizing was first developed in the 1970s but did not become widespread until the 1990s when personal computers became more affordable and readily available.[4] For particle sizing a back-illumination technique is used, with the light source and camera directly opposite each other. The light from the laser is transmitted through a diffuser arrangement, lighting up the area behind the particles. In this way, the camera captures images of the silhouettes of the particles as they move through the measurement zone.

To determine the size, Oxford Lasers *VisiSizer* analysis software measures the shape, area and edge sharpness of the silhouette to identify particles in the images. Once identified, the software determines the position of the particle in relation to the plane of focus by comparing the edge-sharpness to a predetermined calibration, and reports the correct particle size. Particle velocity can be measured by tracking the particle movement between two sequential images.

3. Flow Field Vector Analysis

This technique provides detailed information of the flow velocity in a plane within the flow during an event by using a light sheet configuration similar to the general characterisation setup. To obtain vector information, two sequential images are compared using a cross-correlation technique to measure the particle shift between them. The analysis software divides the images into small integration regions and determines the change in pattern between a pair of adjacent images to report the vector information. Murphy provides more detailed information on image-based techniques.[2,5]

ANALYSIS OF NASAL DEVICES

EnVision provides a unique platform to complete an extensive range of characterisations from straightforward high-speed imaging to the more advanced techniques described above.

Three recent examples demonstrate how the *EnVision* system has been used to assess a nasal spray:

Application 1 – Williams *et al* studied the influence of pump type, actuation operating conditions and type of solution on the aerosol particle velocity.[6]

A high-speed sequence of backlit images (see figure 3) of the device actuation event was acquired, and particle size and particle velocity information collected.

The velocity of the droplets ranged between 1.7 and 28.6m/s. For both nasal spray pump A and pump B the average droplet velocity ranged from 8.4 and 12.8m/s. The advanced particle sizing techniques allowed the user to collect detailed information on size and velocity of the drops in flight to make the necessary comparison (see figure 4).

Application 2 – Williams *et al* set out to look at the variation in the velocity profile at multiple positions in the spray plume for a range of nasal spray pumps.[7]

The Evaluation was carried out using an *EnVision* system using a light-sheet configuration. Oxford Lasers' VidPIV software was used to analysis the pairs of images, using adaptive cross-correlation techniques, to determine velocity vector information.

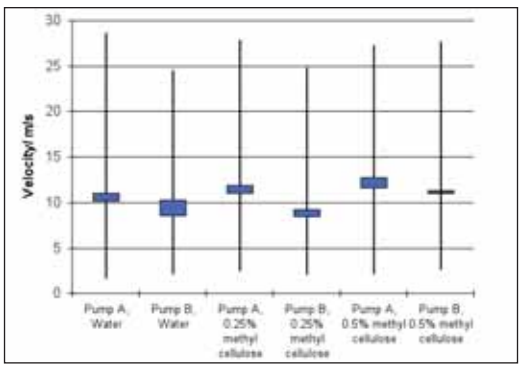

Figure 4: Comparison of two different nasal pumps with three different viscosity solutions in each. Results show that velocity of spray is not affected by solution viscosity.

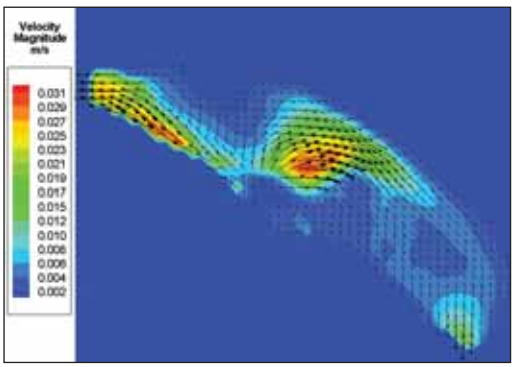

Figure 5: Sample image of flow-field vector information collected inside the nasal cavity

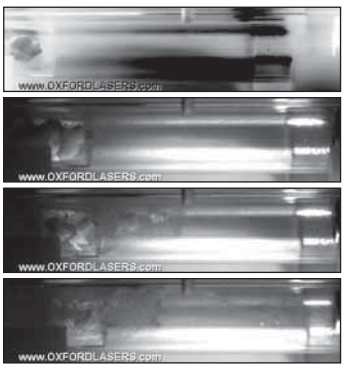

Figure 6: Fracturing behaviour of dry powder, showing powder bed break-up and fluidisation process

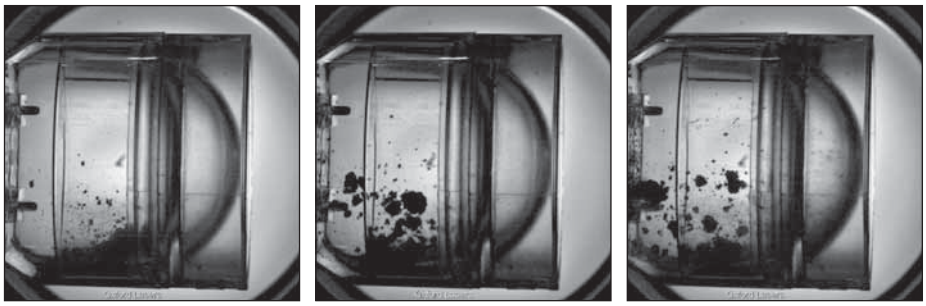

Figure 7: Images showing the movement of powder through a dry-powder device

The average aerosol velocity ranged from 6.8 to 14.6m/s at various positions through the spray. The *EnVision* platform is a unique platform for the characterisation of pharmaceutical nasal spray velocity and can support efforts to meet regulatory requirements. When used in conjunction with other measurement techniques it can provide an understanding of particle transportation and deposition within the nasal cavity.[7]

Application 3 – Doorly *et al* completed extensive studies on the flow regimes through nasal passages.[8]

The study focused on the complex geometry of the nasal passage and how it controls the airflow in various physiological functions. Since the nasal passageway has complex morphology and is inaccessible, detailed *in vivo* measurement was not possible. As a result the only way to investigate the problem, was using computational simulation and *in vitro* experiments.

A replica model of a nasal cavity was produced and derived from *in vivo* scans. General high-speed imaging techniques and flow-field vector analysis were used to investigate the flow through the nasal passage.

The flow field vector technique with controlled artificial seeding was shown to provide quantitative measurement of the flow velocity (figure 5), with peak velocities of 3 m/s.

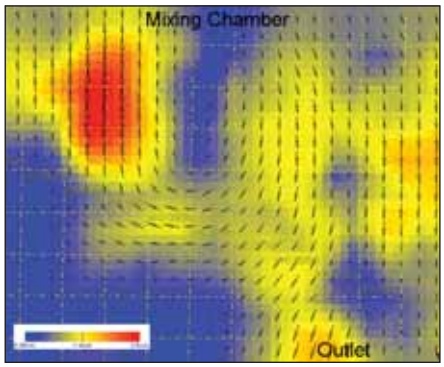

Figure 8: Flow-field map of the flow inside a dry-powder device and as the powder is ejected. Velocity range in this application 0.0 to 2.8m/s.

ANALYSIS OF A DPI

EnVision systems, with their combination of high-speed imaging and advanced analysis techniques are proving invaluable tools in the understanding of DPIs.

Extensive studies by R Price and J Shur have investigated the effect of different powder formulations on system performance by examining fluidisation and deaggregation of the powder. [9-11] In figure 6 the *EnVision* high-speed imaging system was used to acquire images of the fluidisation process at 8,000Hz to show how the powder bed fractures.

DIRECT EVALUATION OF THE FLOW OF POWDER INSIDE A DPI

Advanced imaging and illumination techniques make it possible to see how the powder is fluidised, entrained and expelled from a DPI system. Figure 7 shows how a back-illumination technique can reveal initiation of the process. As powder is drawn from the system the images show how the powder bed is broken up and how fluidisation and entrainment of the powder in the airflow occurs.

With light-sheet illumination, flow-field vector analysis can be applied to determine the flow-velocity profile inside the dry-powder system. Figure 8 illustrates how the flow rotates inside the chamber before being drawn out through the outlet into the patient

SUMMARY

Advanced image-based systems such as the *EnVision* system are providing unique information to aid the understanding and development of both nasal and dry-powder devices. The combination of short pulse-duration laser light sources and high-quality images allow users to access more powerful analytical techniques not traditionally used within the pharmaceutical industry. Furthermore, these techniques are a useful platform to support efforts to meet regulatory requirements. [7]

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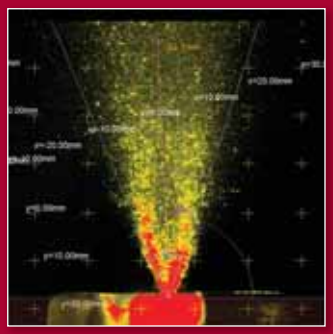

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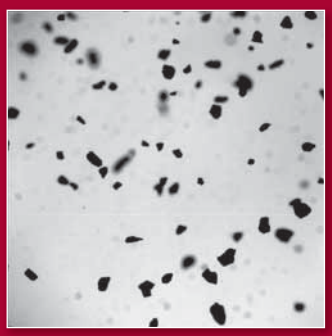

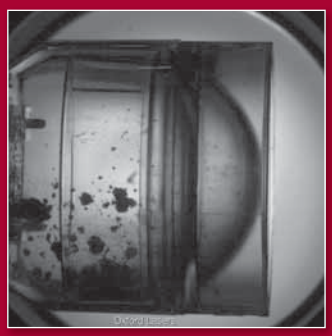

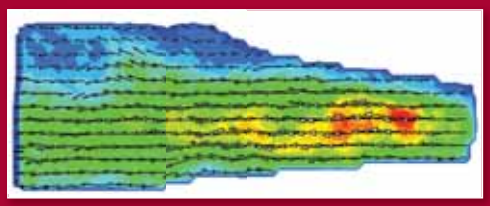

Flow Field Vector Analysis

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- See time-resolved flow development

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Büchi's latest instrument generation – the Nano Spray Dryer B-90 – revolutionises spray drying with an innovative technology for particle creation down to the submicron and even nanometre range from minimal sample quantities at highest yield.

Spray drying becomes increasingly important in drug development, formulation and particle design as a gentle, easy-to-control, continuous and scalable process to convert liquid formulations directly dry powders.

The Nano Spray Dryer B-90 is especially designed for the early stages of product development. The modular glass assembly enables a visible spray process and a quick and gentle drying of various applications in small scale, ideal for feasibility studies in R&D laboratories to dry only a few millilitres of substance.

The Nano Spray Dryer B-90 meets the requirements of the pharma, biotech, medical, food ingredient, chemical and advanced material industry as well as nanotechnology. New application trends focus on effective formulation of complex pharmaceuticals and nanomaterials for novel drug delivery systems, like inhalable powders. Typical applications are spray drying of aqueous or solvent based solutions, nano-emulsions, nanoparticle suspensions, structural transformations or nano-encapsulations.

The droplet generation is based on a piezoelectric driven actuator, vibrating a thin, perforated membrane in a small spray cap. The membrane features an array of micron-sized holes. The actuator is driven at ultrasonic frequency, causing the membrane to vibrate, ejecting every second millions of precisely sized droplets with very narrow droplet distribution. Different spray caps with 4.0, 5.5 and 7.0µm hole sizes are available to achieve a precise droplet size between 8 and 21µm.

Büchi's Nano Spray Dryer B-90

A unique heater technology based on porous metal foam provides a laminar gas flow in the drying section. Optimal energy input guarantees fast heat-up times up to 120°C for very gentle drying of heat-sensitive materials.

The fine spray dried particles are separated by an electrostatic particle collector, a novel technology in laboratory scale. The electrostatic particle collector offers excellent particle recovery rates for samples in the milligram range. It enables an easy collection of small powder amounts of high value materials at high yields.

The integrated LCD display ensures easy process control. The PC software provides comprehensive data acquisition, storage and export capabilities. The transparency from spray head to particle collector due to the glass assembly and the very short set-up times enable an easy cleaning and even sterilisation.

- Produce finest particles of 300nm to 5µm size with very narrow size distribution
- Dry samples in the milligram range
- Profit from minimal product loss due to uniquely high yields up to 90%
- Save process time thanks to quick assembly, easy cleaning and fast product change

Since 1979, BÜCHI Labortechnik AG offers the Mini Spray Dryers B-190, B-191 and B-290 and is the worldwide market leader in laboratory scale spray dryers. Over 2900 units have been installed at universities, R&D centres and powder specialists around the world.

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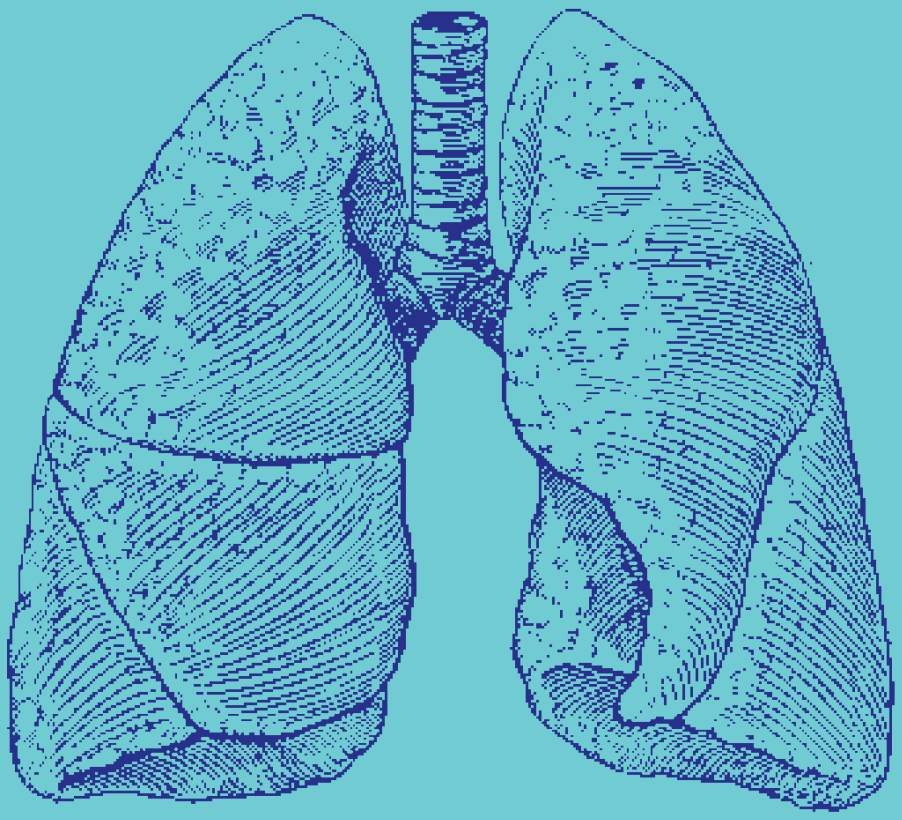

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