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Pulmonary & Nasal Drug Delivery

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Front cover image: "CFD plot showing flow streamlines coloured by velocity magnitude, m/s,in a high-efficiency swirl chamber," supplied by Team Consulting (see this issue p10). CFD work carried out by Stuart Abercrombie. Reproduced with kind permission.

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Aptar Pharma: your global solution provider of innovative and proven aerosol, injection, spray and dispensing systems.

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PULMONARY DELIVERY OF ANTIMICROBIAL PEPTIDES

Anna Fureby, PhD, Group Manager & Senior Scientist, Life Science, and Ulla Elofsson, PhD, Senior Scientist, both of SP Technical Research Institute of Sweden, and Per Gerde, PhD, Chief Scientific Officer, Inhalation Sciences Sweden, discuss the serious problem of antibiotic resistance and the potential role of antimicrobial peptides in the treatment of resistant bacterial strains. For pulmonary infections, optimising the formulation and delivery method is a crucial factor for success.

Resistance to traditional antibiotics is a rapidly increasing problem that in a few years could make infections impossible to treat and bring the state of medical care back to the pre-antibiotic era from the beginning of the last century. Antimicrobial peptides (AMPs) have a huge potential as new therapeutics against infectious diseases as they are less prone to induce high-level resistance due to their fast and non-specific mechanism of action.

> "To date, no products based on AMPs have reached the market. One of the main reasons is the challenge related to stability of peptides during storage as well as after administration"

A NEW APPROACH TO BACTERIAL LUNG INFECTION – FORMAMP

A large variety of AMPs have been identified and isolated from plants, animals and humans and their structure is well preserved. These have also been assessed, analysed and modified in order to increase their function and efficiency for drug delivery applications. These peptides act by interacting with the bacterial membranes and by perforating the membrane (see Figure 1). However, only a few candidates have reached late stages of clinical trials and, to date, no products based on AMPs have reached the market. One of the main reasons is the challenge related to stability of peptides during storage as well as after administration, which dramatically reduces the efficiency.

These challenges are addressed in "FORMAMP – Innovative Nanoformulation of Antimicrobial Peptides to Treat Bacterial Infectious Diseases", a large collaborative project within EU's NMP-programme. The aim of FORMAMP is to explore innovative nanoformulation strategies to formulate well-characterised AMP candidates in order to improve the efficiency and stability of the peptides in clinical development. In addition, the nanocarriers are formulated in functional dosage forms, i.e. for pulmonary delivery for local treatment of bacterial infections.

Different nanoformulation platforms, particularly promising for peptide delivery, controlled-release strategies and technologies against proteolytic degradation of peptides will be evaluated in the project. These include carriers of organic origin (lipid-based and polymer-based systems) as well as inorganic carriers (nanostructured silica). The effect of nanoformulated AMPs will be evaluated with state-of-the-art *in vitro* and *in vivo* models. The results of this interdisciplinary project will generate efficient treatment strategies combatting one of the largest threats to our healthcare system and society today, reducing healthcare costs and expanding the growth of European enterprises within the field of pharmaceutics and nanomaterials.

TB & CF – DISEASES IN NEED OF NOVEL COMPLEMENTING MEDICATIONS

A wide-spread, but usually curable pulmonary disease is tuberculosis (TB). About 2 billion people are infected by *Mycobacterium tuberculosis* (MTB) and, in 2012, 8.6 million people developed tuberculosis.[1] The bacterium infects when it is inhaled and subsequently reaches the alveoli, where the bacilli are phagocytised

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and accumulate in alveolar macrophages, the cells form a hard shell (granuloma) that keep the bacilli contained, and can survive in a dormant state for years. If the MTB overcome the immune system of the infected individual, the infection progresses as the bacteria multiply rapidly, so that TB develops. The patient is infectious at this time.

Most cases of TB are pulmonary but it can occur in almost any anatomical site. In recent years, drug-resistant TB has become more widespread, which makes treatment of the disease more complex. Already, drug-sensitive TB requires a treatment period of about six months using different combinations of antibiotics.

Cystic fibrosis (CF) is an autosomal recessive genetic disorder that affects mainly the lungs but also the pancreas, liver, kidneys and intestine. It is caused by the presence of mutations in both copies of the gene for the protein cystic fibrosis transmembrane conductance regulator (CFTR). The production of sweat, digestive fluids and mucus is influenced by CFTR so that the viscosity of these secretions is increased. The disease is most common among people of European ancestry, and affects around 70,000 people worldwide. In Europe, approximately 1 in 3000 newborn infants is diagnosed with CF. The average life expectancy is between 37 and 50 years in the developed world, and the major cause of deaths is lung problems.

A particular problem that occurs in addition to repeated lung infections is the excessive and sticky mucus in the lung and the generation of biofilms that are colonised by different bacteria, such as *Pseudomonas aeruginosa, Staphylococcus aureus,* and *Haemophilus influenza*. When located in the biofilm, the bacteria tend to develop antibiotic resistance and also become less available for the drugs, administered orally or by inhalation.

Thus, for both MTB and CF there is a need to find novel treatments that can

Figure 1: Nanocarriers investigated in FORAMAMP for delivery of antimicrobial peptides to the lungs for treatment of tuberculosis associated with granuloma and cystic fibrosis associated with biofilm.

penetrate into the granuloma or into the biofilm to reach the bacteria and take effect. For both diseases, development of antibiotic-resistant strains of bacteria is a common and increasing problem. Current research addresses this issue by, for example, developing nanoformulations of established active substances to enhance their effect.

As mentioned above, an attractive alternative to conventional small-molecule antibiotics is antimicrobial peptides. In

NANOCARRIERS FOR PULMONARY DELIVERY OF PEPTIDES

As soon as they enter the body, AMPs, as well as other peptides and proteins, are attacked by proteases, which break them down into amino acids and shorter fragments. Further, the complicated structures make them sensitive to breakdown during storage where interactions with device surfaces, air/water interfaces, presence of enzymes, may result in loss of the effect.

"The results of this interdisciplinary project will generate efficient treatment strategies combatting one of the largest threats to our healthcare system and society today"

FORMAMP antimicrobial peptides are used that have demonstrated activity towards bacterial strains (including some drug-resistant strains) such as *P. aeruginosa*, *S. aureus* and *M. tuberculosis*, without showing negative effects on human cells. In order to make these available as medications, nanostructured formulations are necessary.

Combining peptides with a (nano)carrier can protect the peptide from the proteolytic attack and also provide prolonged or triggered release.

For inhalation therapy, the inhaled particles or droplets need to be in the respirable size range, 1-5 µm, and thus the peptides must be formulated to meet this requirement. The

A: mesoporous silica particles with AMP in the pores
B: nanogels with AMP in the cross-linked polymeric network
C: Dendrimers that bind AMP
D: Lipidic nanocaprusles that can either contain AMP in the interior or on the surface
E: liquid crystalline nanoparticle with AMP in the internal structure of on the surface

Figure 2: Schematic illustration of the possible action mechanisms of antimicrobial peptides interacting with cell membranes.[13]

One of the most studied concepts is liposomes, which are able to hold active substances inside as well as in/on the surface of the liposomes. These have mostly been studied in nebulised form with success at least in animal models, but few studies of dried liposomes are available.[1] In order to increase their residence time in the lung, liposomes have been modified with, for example, chitosan.[3]

Alternative nanoparticles for drug delivery are e.g., PLGA particles, alginate-chitosan hybrid particles,[5] and hyaluronan particles,[6] which all provide longer residence time in the lungs.[7,8]

In general, studies using animal models have shown that the therapeutic index can be improved and the dose to reach the local MIC can be reduced when nanoformulations are used.

Peptides that attack *P. aeruginosa* and other species in biofilms associated with CF need to penetrate the matrix of the biofilm. This is composed of polysaccharides and DNA, which both increase the viscosity. Positively charged polymers can help break up the biofilm matrix. Liposomes and PLGA particles have been studied by several groups and, when tested, the antimicrobial efficiency compared with free drug has been enhanced in most cases. It has been shown that the surface charge of liposomes is important for the delivery of the drug, so that positively charged liposomes are more efficient than negatively charged, whereas neutral liposomes do not penetrate the biofilm.[9]

However, other studies show that neutral liposomes can be efficient in delivering antibiotics in cystic fibrosis biofilms.[10] Hybrid particles composed of a PLGA core and a lipid coating has also been investigated with enhanced drug delivery in biofilms.[11]

The effect of the nanoformulated AMPs in FORMAMP will be evaluated with state-of-the-art *in vitro* models and *in vivo* models. These models include macrophage exposure models for anti-TB assessment, and a biofilm model where a controlled biofilm can be grown, evaluated for structural changes and viability after delivery of AMP, and be exposed to labelled particles which are tracked to enable evaluation of the penetration into the biofilm. Initial results from in vitro models are promising and show in most cases that the AMP is preserved and in some cases even improved by the presence of nanoformulations.

Most of the excipients used in nanoformulations are not approved for pulmonary

preferred delivery form is inhaled powders, as this enables high drug concentrations and the lengthy inhalation time of nebulisation is circumvented. Dry formulations also bring the advantage of increased storage stability even at room temperature. An additional problem that can be encountered in nebulisation is that the peptides are damaged during the droplet formation. Different nanoformulation platforms, particularly promising for peptide delivery, controlled-release strategies and technologies against proteolytic degradation of peptides will be evaluated in the project. These include lipid-based systems such as lipidic nanocapsules and self-assembled lipid nanoparticles, polymer-based structures such as dendrimers and microgels as well as nanostructured mesoporous silica, schematically illustrated in Figure 2.

The peptides in FORMAMP are new, but peptides for other medical uses have been under investigation for a few decades, as the lung is a suitable route for systemic delivery without first-pass effects.

The most studied peptide for pulmonary delivery is insulin, for which rapid systemic delivery is the target. Such a product was on the market for a short period in 2006/2007. For improved delivery and to avoid phago-

cytosis insulin was spray-dried as larger very porous particles (Pulmospheres®). Recently, the US FDA approved a new insulin formulation for inhalation that is produced and marketed by MannKind Corporation (Valencia, CA, US) and Sanofi (Paris, France). Insulin is formulated with fumaryl diketopeperazine as the carrier, which self-assembles through hydrogen bonding in mildly acidic environment to form microspheres (Technosphere®).

When addressing tuberculosis via pulmonary delivery, the specific target is the macrophages that carry the MTB inside. Therefore phagocytosis is desired in contrast to e.g. insulin delivery. Literature indicates that infected macrophages have higher phagocytic activity compared with uninfected macrophages, which may be used to improve targeted delivery.[2] For efficient uptake in the macrophages the microparticle should have the appropriate size and surface characteristics. The optimal size is about 3 μm (range 1-10 μm).

Nanoformulation concepts used for pulmonary delivery of various small-molecule TB drugs such as rifampicin may be possible to translate to peptide delivery, although this has not been tested yet.

delivery, thus the introduction of these formulations will necessitate regulatory approval. This may constitute a hurdle to the introduction of these novel formulations, but it needs to be overcome to make new and innovative therapies available to the patients in need.

EVALUATION OF POTENTIAL FOR PULMONARY DELIVERY

In order to be efficacious for treating pulmonary diseases, nanoformulated peptides need to be delivered in the right area of the lung. During development of new formulations for pulmonary delivery of peptides it is critical to evaluate these under sufficiently *in vivo*-like conditions. In creating a carrier aerosol two parameters are of cardinal importance for performance:

1) the aerodynamic particles size distribution combined with the ventilation manoeuver will determine the prime region of exposure in the respiratory tract
2) the release characteristics of the therapeutic peptides from the carrier formulation will influence the delivery rate of the peptides to the surrounding lung tissues.

To evaluate these properties fully it is of great value if the same aerodynamic aerosol can be delivered to several complementary exposure modules, including the standard cascade impactors for assessment of aerodynamic particle size. To this end the PreciseInhale™ platform is used,[12] consisting of a series of exposure modules from cascade impactors, cultured lung epithelial cells, isolated perfused rodent lungs to tracheally intubated-, or nose-only rodents can be exposed to the very same aerosol formulation throughout.

For soluble peptides there is a rapidly decreasing rate of absorption in the lungs with increasing molecular weight. So for smaller peptides nanoformulations can be used both to decrease the absorption rate in the lungs thereby increasing effect duration, and to protect the peptides from enzymatic degradation in the lungs. The two exposure models most useful for detecting the inhalation pharmacokinetics of the various formulations is the isolated ventilated and perfused lung of the rat (IPL), and the intratracheally intubated rat (IT). The IPL provides a high resolution absorption curve of the peptide into the circulation for up to three hours after exposure. The IPL model can be very useful when comparing the absorption rate of a peptide formulated as

neat powder or when incorporated into various more advanced nanoformulations. These exposures should be complemented with intratraecheal exposures to the same formulations revealing the systemic distribution of the inhaled compounds for longer periods after inhalation. A third model that could be of interest for deriving comparative data is by exposing to the same aerosols airway epithelial cells that are cultured at airlifted conditions in Transwell inserts and perfused in single-pass mode. This could derive valuable data from a 3R (replacement, reduction and refinement) standpoint.

CONCLUSION

In summary, novel nanoformulations have been shown to be promising for the delivery of small-molecule antibiotics to treat both tuberculosis and cystic fibrosis. A particular advantage is the possibility for local drug delivery in the lung. The extension of using similar nanoformulation platforms for delivery of antimicrobial peptides holds promise for the future and is currently under development in FORMAMP. The development of such novel formulations will necessitate regulatory approval of excipients new to pulmonary delivery as well as of the antimicrobial peptides.

ACKNOWLEDGMENT

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THE ADVANTAGES OF DESIGNING HIGH-RESISTANCE SWIRL CHAMBERS
FOR USE IN DRY-POWDER INHALERS

In this article, David Harris, Head of Respiratory Drug Delivery, Team Consulting, taps into a powerful combination of detailed anatomical and functional understanding of the human respiratory system, pulmonary drug delivery technology and formulation expertise, and mathematical modelling techniques, in order to put forward the case for high-resistance swirl chambers in dry-powder inhalers, and a rational strategy for optimising the design and thus maximising therapeutic efficacy.

WHY IS HIGH RESISTANCE GOOD FROM A PATIENT'S PERSPECTIVE?

A question dry-powder inhaler (DPI) device developers always face is: "What airflow resistance should I make the device?" Many studies have been conducted and the results often published, but there still appears to be no commonly agreed answer about what is best. The airflow resistance of the pressurised metered dose inhaler (pMDI) is rather arbitrary, as pMDIs produce a respirable aerosol completely independently of how the user inhales. DPIs, on the other hand, rely solely upon the energy available in the user's inspiratory manoeuvre – some of which is transferred into the bulk powder to transform it into a respirable aerosol.

There are several performance factors that are directly affected by the resistance of a DPI…

1. Pressure Drop

All inhaler users will achieve a higher pressure drop across the device when inhaling through a higher-resistance DPI. This is because users achieve their highest inspiratory flowrate under no load (zero resistance); and their highest inspiratory pressure drop under maximum load (infinite resistance). And there is a reasonably linear response between these two extreme scenarios. Achieving a high pressure drop is key to creating an efficient aerosolisation engine, and to producing a high fine particle fraction (FPF), as it is the inspiratory pressure drop that provides the force necessary to create high-velocity airflows within the inhaler.

2. Consistency

The lungs of children and COPD patients are powered by muscles that are more or less as strong as a healthy adult's. This means that, on average, all three patient groups converge toward a common peak maximal inspiratory mouth pressure, which is the maximum pressure drop they can achieve across an infinite resistance device (i.e. zero flow). However, their maximal inspiratory capacity is significantly less than a healthy adult's; a child's because their lungs are not yet fully grown, and a COPD patient's because some proportion of their lungs no longer function normally. Data shows that as the device resistance decreases, users with higher usable lung capacity can achieve higher inspiratory flowrates, and the pressure flow curves of children and adults (for example) diverge (Figure 1).[1]

3. Duration of Inhalation

As users achieve lower flowrates through higher-resistance inhalers, it takes more time to fill their lungs and so the duration of inhalation is increased.

4. Lung Deposition

The air velocities within their oropharynx, upper airways and bronchioles within the lungs will be lower when inhaling through a high-resistance device due to the limited maximum inspiratory flowrate that can be achieved. These lower airflow velocities are less likely to cause inertial impaction of respirable particles, which results in an aerosol of a given particle size distribution penetrating deeper into the lungs, and a greater overall therapeutic effect.[2]

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THERE IS NO "TYPICAL" DPI RESISTANCE

DPIs that are commonly prescribed today have a large range of resistances, ranging from Plastiape's low-resistance Cyclohaler® to Boehringer Ingelheim's high-resistance HandiHaler®. The airflow resistance of an inhaler is defined as the square-root of the pressure drop divided by the flowrate, assuming turbulent flow. Various units are used, but a sensible approach is to use √Pa for pressure drop and litres per minute (LPM) for flowrate, as this produces numbers of a reasonable magnitude for the resistance. For example, the HandiHaler has a flowrate at 4 kPa (Q_{out})[3] of approximately 30 LPM, so its resistance is calculated as follows:

$$R = \frac{\sqrt{\Delta P}}{Q} = \frac{\sqrt{4000}}{30} = 2.11 \sqrt{Pa} \min L^{-1}$$

The units of resistance are awkward and not particularly memorable, so from this point onward, I will refer to √Pa min L⁻¹ as "Flohms", or FΩ – a combination of "flow" and "ohms", and a lot easier to write (and pronounce). The Cyclohaler has a much lower resistance, with a Q_{out} of approximately 110 LPM, so a resistance of 0.57 FΩ.

It should be noted that a better method to determine the airflow resistance of an inhaler is to create a pressure-map, i.e. record the steady-state flowrate through the device for a range of pressure drops up to approximately 10 kPa, as this corresponds to the likely range in real use. A graph is then plotted of √ΔP against Q (the pressure map), and a linear regression calculated (forced through the origin); and the gradient of this line is the airflow resistance of the device.

WHAT FLOWRATES ARE ACHIEVED THROUGH DPIS IN REAL USE?

The US Pharmacopeia (USP) instructs *in vitro* tests to be carried out at a nominal flowrate, Q_{out}, which corresponds to a 4 kPa pressure drop across the device. In reality, however, it is a little more complicated – in that the pressure drop achieved by the user is highly dependent upon the airflow resistance of the device. Most users following typical DPI instructions for use (IFUs) will achieve higher inspiratory pressure drops than the 4 kPa test point prescribed in the USP – particularly for high-resistance devices.

The pressure-flow curves of the three example DPIs have been overlaid on the data in Figure 1, and the average operating points for healthy adults and children can be
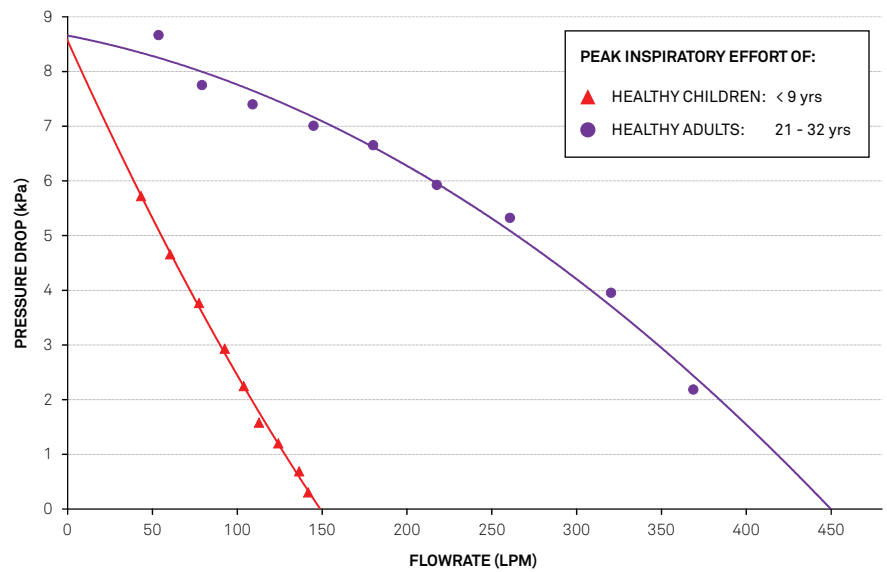

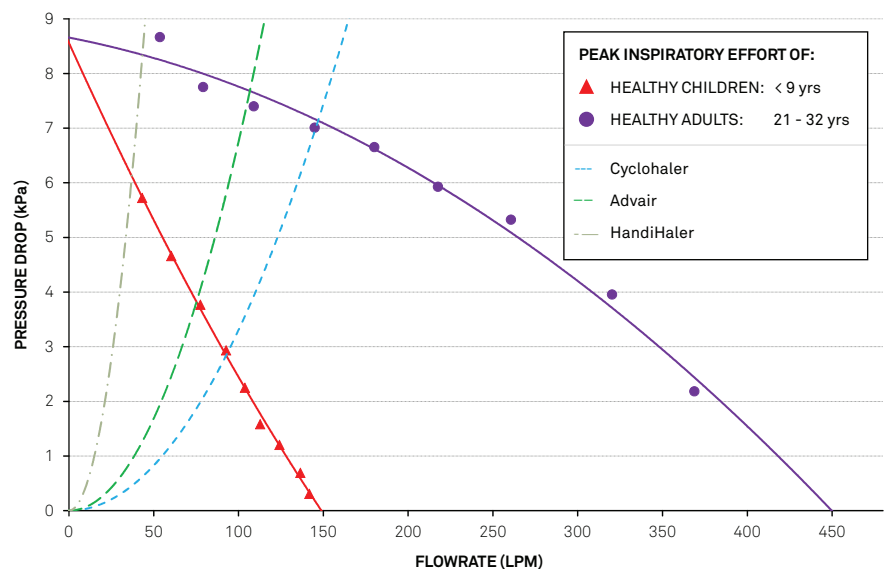Figure 1: Effect of age on inspiratory flow characteristics.

Figure 2: Estimated operating points of DPIs when used by healthy adults & children.

estimated from the intersections of the curves (Figure 2).

Healthy adults are able to achieve very high pressure drops even across the lowest-resistance DPIs when instructed to inhale with maximum effort. Even the low-resistance Cyclohaler is likely to see a pressure drop of approximately 7 kPa in real use; significantly higher than the nominal 4 kPa test point. The high-resistance HandiHaler is likely to see over 8 kPa when used by healthy adults, and ~6 kPa when used by healthy children.

It is also interesting to note that inhaler resistance has a greater effect on the likely operating pressures for children than for adults (Figure 2).

So whilst there is currently no common agreement about the optimal airflow resistance for DPIs, in terms of reaching maximum performance and greatest consistency between users, high resistance is most likely to achieve this, because users achieve higher pressure drops across higher-resistance devices; and the difference in the pressure drop achieved across a high-resistance device is minimised between user groups.

HOW IS THIS APPLICABLE TO SWIRL CHAMBER DESIGN?

Swirl chambers have been successfully utilised in numerous DPIs to de-agglomerate fine API particles from the much coarser lactose "carrier" fraction. Almiral's Novolizer® DPI uses a powerful multi-inlet swirl chamber; a similar design was later optimised for use in Sun Pharma's Starhaler®, with a spe-
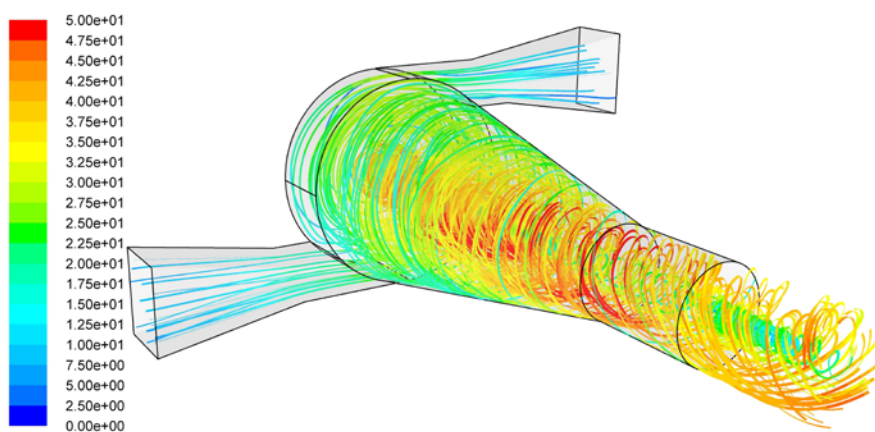
Figure 3: CFD plot showing flow streamlines coloured by velocity magnitude, m/s, in a high-efficiency swirl chamber (CFD work conducted by Stuart Abercrombie, Team Consulting).

cific geometry employed to create excellent independence of flowrate.

Other DPIs that use swirl chambers are 3M's Conix® device, which employs a reverse-flow cyclone to achieve high de-agglomeration efficiency, and the Twincer® DPI, that uses a pair of swirl chambers that are flat in order to minimise the thickness of the device.

Swirl chambers have many advantages over other de-agglomeration methods:
• With good design they can be self-cleaning – in that the lactose scours the boundary layer and prevents API build up in it, minimising the likelihood of dose "spikes".
• They create multiple impacts, which results in a high frequency of collisions and more opportunities for API detachment – and consequently better aerosolisation and a higher fine particle fraction (FPF).
• The conservation of angular momentum in a conical converging section creates a highly swirling flow regime, which imparts energy into the formulation efficiently.

The computational fluid dynamics (CFD) plot (Figure 3) shows flow streamlines coloured by velocity magnitude through a twin-inlet, high-efficiency swirl chamber, and illustrates the gains that can be achieved due to the conservation of angular momentum, with peak tangential velocities occurring towards the narrow outlet of the chamber.

We set about a hypothetical challenge of creating a high-performance swirl chamber

to promote good de-agglomeration efficiency of a reference lactose-based formulation. We chose a number of realistic design constraints then mathematically modelled the airflow through the swirl chamber in order to create optimised geometries that would have the properties summarised in Figure 4.

DESIGN CONSTRAINTS

As there will always be limited space for a de-agglomeration engine within a reasonably sized DPI we chose to use the space envelope as the primary design constraint for our mathematical model:
• Fixed space envelope – cylinder of diameter 14 mm and length 33 mm
• Two square, tangential air inlets
• Throat (outlet) area = 1.25x total inlet area
• Parallel section of throat fixed at 5.00 mm.

SWIRL CHAMBER GEOMETRIES

To a skilled cyclone engineer it is clear that increasing the device resistance, whilst abiding by the above design constraints, creates a more "normal" looking swirl chamber, in terms of cone angle and inlet / outlet size in relation to the swirl chamber body (Figures 5-7). A good swirl chamber will maximise swirl velocity in the throat (the most constricted region) through conservation of angular momentum. To achieve this the out-

let diameter must be substantially smaller than the body diameter – which is not possible for the low-resistance design (Figure 7).

WHAT IS "IMPULSE HISTORY", AND HOW IS IT INFLUENCED BY SWIRL CHAMBER GEOMETRY?

The parameter "Impulse History", I, has been used successfully as a proxy for aerosolisation performance in previous studies.[4] In a swirl chamber the momentary impulse for a single lactose particle passing through the region of high swirl has been defined according to the following integral over time:

$$I = \int F dt \propto \int |u|^2 dt \propto \int \left(\frac{\Delta u_{ax}^2 + \Delta u_{\theta}^2}{r_r} + |u|^2 \right) dt$$

- Equation 1

The centrifugal force acting upon the lactose particle is represented by the first term, with the second representing the aerodynamic drag force. Rearranging for path length S gives the Impulse History as:

$$I' \propto \int_{Cone} \left(\frac{\Delta u_{ax}^2}{r|u|} + |u| \right) dS_1 + \int_{Cone} \left(\frac{\Delta u_{\theta}^2}{r|u|} + |u| \right) dS_2$$

- Equation 2

The Impulse History is a quantity that is proportional to the actual impulse, and serves as a useful proxy for the aerosolisation performance of the swirl chamber.

In simple terms, why does increasing resistance increase the Impulse History?
• Like in Dyson (Malmesbury, UK) vacuum cleaners, reducing the size of the swirl chamber (cyclone) increases the pressure drop required to achieve a given flowrate – i.e. its resistance increases, which is why Dyson uses multiple cyclones configured in a parallel array.
• For a given pressure drop the net inlet and outlet velocities will be very similar between geometries as the swirl chamber reduces in size. As the outlet diameter reduces, the centripetal acceleration acting on particles in this region increases, as the acceleration is proportional to the square of the (tangential) velocity over the radius. So for the same operating pressure, smaller, higher-resistance swirl chambers create higher centripetal accelerations.
• In a given space envelope and as the resistance increases, the designers can afford a greater difference between the swirl chamber body diameter and the outlet diameter, and due to this, conservation of angular

Resistance →	High	Medium	Low
Example device →	HandiHaler	Advair®	Cyclohaler
Q_out →	30 LPM	77 LPM	110 LPM
R →	2.11 FΩ	0.82 FΩ	0.57 FΩ

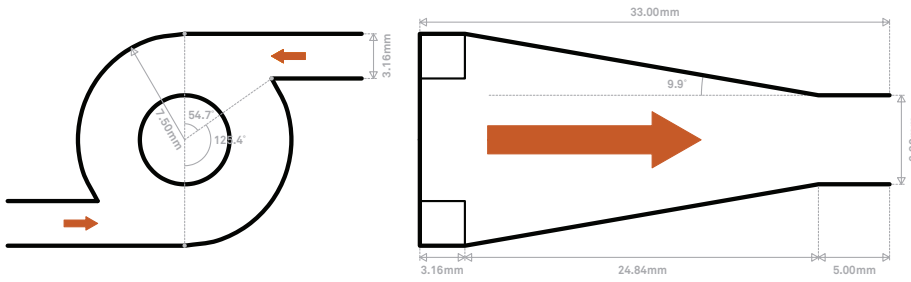Figure 4: Summary of example high-, medium- and low-resistance devices.

Figure 5: Optimised twin-inlet swirl chamber: High resistance, e.g. HandiHaler.
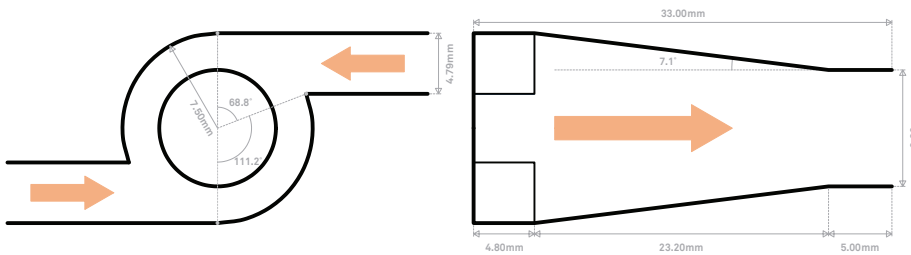

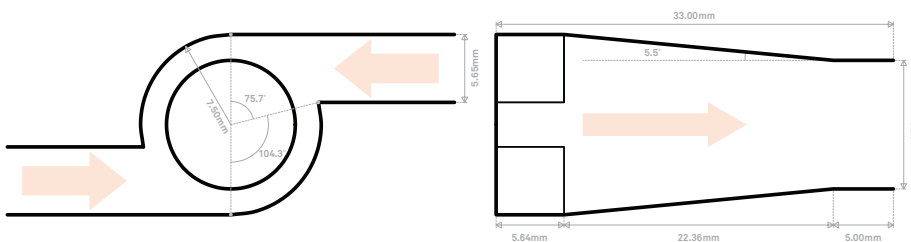Figure 6: Optimised twin-inlet swirl chamber: Medium resistance, e.g. Advair.

Figure 7: Optimised twin-inlet swirl chamber: Low resistance, e.g. Cyclohaler.

CONCLUSION

It is anticipated that the order of magnitude increase in Impulse History – that can be achieved by designing a high-resistance swirl chamber – is likely to result in a significant improvement in de-agglomeration performance and associated therapeutic effect.

In order to explore this hypothesis, it is proposed to prototype three different swirl chamber geometries for *in vitro* evaluative testing. This will enable an assessment for correlation between the performance predicted by the mathematical model and empirical data to be made.

Assuming that, as with previous studies, the predictions prove to be sufficiently accurate, this could represent a very worthwhile opportunity for improving DPI performance and the therapeutic effect for patients.

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momentum leads to increased swirl velocities in the most constricted region. As the centripetal force acting upon the lactose particles is proportional to the square of the tangential (dominant) component of the swirl velocity, this also increases, leading to a greater Impulse History.

PREDICTED RESULTS

At an operating pressure of 4 kPa an eight-fold increase in the Impulse History is predicted by the model, from the low- to the high-resistance geometry (Figure 8). As discussed earlier, it's likely that even children are able to create higher driving pressure drops when instructed to inhale with maximum effort. Predicting the Impulse History at typical healthy adult and child operating pressure drops leads to an even greater difference, with the high-resistance geometry achieving an order of magnitude improvement over the low-resistance design (Figures 9 and 10).

Figure 8: Average Impulse History predicted at 4 kPa for the three different resistance swirl chambers.

Figure 9: Average Impulse History predicted at healthy adult operating points, for the three different resistance swirl chambers.

Figure 10: Average Impulse History predicted at healthy child operating points, for the three different resistance swirl chambers.

ONdrugDelivery 2015 EDITORIAL CALENDAR

Publication Month	Issue Topic	Materials Deadline
May 2015	Injectable Drug Delivery: Devices Focus	April 13th
June 2015	Novel Oral Delivery Systems	May 4th
July 2015	Wearable Bolus Injectors	June 1st
October 2015	Prefilled Syringes	September 7th
November 2015	Pulmonary & Nasal Drug Delivery	October 5th
December 2015	Delivering Biotherapeutics	November 9th
January 2016	Ophthalmic Drug Delivery	December 14th
February 2016	Prefilled Syringes	January 11th
March 2016	Transdermal Delivery & Microneedles	February 8th
April 2015	Pulmonary & Nasal Drug Delivery	March 7th

INVESTIGATING THE DE-AGGLOMERATION PROFILES
OF DPI FORMULATIONS

In this paper, Srinivas Ravindra Babu Behara, PhD, Researcher; David Morton, PhD, Associate Professor; Ian Larson, PhD, Senior Lecturer; and Peter Stewart, PhD, Deputy Dean & Professor of Pharmaceutical Sciences, all of Monash University; and Paul Kippax, PhD, Product Group Manager, Malvern Instruments, describe the use of laser diffraction to analyse dry powder behaviour. The authors introduce relative de-agglomeration versus flow rate profiles, which represent an effective graphical means to summarise the outcome of the complex interplay between the applied aerosolisation energy and the cohesive forces opposing dispersion in different powder formulations emitted from different inhalation devices. The resulting data can be used as a screening method for developing a formulation strategy for a particular active substance.

Despite extensive research efforts, the relative efficiency with which current dry-powder inhaler (DPI) products deliver drugs remains relatively low. Estimates suggest that most commercial products deliver less than 20% of the emitted dose to the lung

"Potential strategies to improve drug delivery include reducing the strength of particle-particle interactions or increasing the intensity of the dispersion process for higher energy impaction. One way to support research in this area is to look at the strength of individual particle-particle interactions"

during routine use.[1] The key to better performance is achieving more informed control of the powder aerosolisation and dispersion processes, as driven by the inhalation effort of the patient. This should ensure that the device and formulation are well matched and optimised. Analytical techniques that support these goals are essential.

DPI formulations have, by necessity, relatively fine drug particle sizes, since only particles of around 5 μm or smaller will penetrate to the lung. Rather than existing as dispersed particles, within the DPI device these micronised, cohesive particles form a continuous networked structure. Packing fractions and interactive forces vary throughout the powder bed and may change during the aerosolisation process. For these reasons analysing the behaviour of the bulk powder bed is a logical approach, and more realistic than investigating and modelling individual particles.

Using the technique of laser diffraction (see Box 1), particle size can be measured in real-time during a DPI actuation. In recent work [2,3] laser diffraction has been used to measure the de-agglomeration behaviour of model DPI formulations over a very broad range of flow rates (30-180 L/min), during dispersion with a commercial device. The resulting data aid understanding of the process and quantify the extent of powder de-agglomeration, providing a new tool for characterising bulk powders and passive DPI performance better.[4,5,6]

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	Dv10 (µm)	Dv50 (µm)	Dv90 (µm)	FPF
Salbutamol Sulphate	0.3	3.4	7.8	75.10%
Lactohale 300	0.2	4.1	9.1	64.80%

Figure 1: Primary particle size data obtained for each of the model formulations. The FPF in this case is defined as the volume% below 5.4 µm in size.

THE MECHANISMS OF DISPERSION

The particle-particle interactions between particles in the sub-5 µm region can be very strong, being driven by electrostatic forces, contact potentials, and intermolecular and capillary interactions.[7] Loaded into a capsule or device, these particles will therefore form a powder bed network, with the strength of interactions being influenced by physical properties such as the particle morphology,[8] surface energy and surface composition.[9] Variations in crystallinity [9] and adsorbed impurities will introduce non-homogeneity into the drug particle population, which may also influence the strength of particle-particle interactions across the network. The microstructures that result range from loosely adhered groups of particles to tightly bound agglomerates.

Delivery of a DPI dose involves two steps: entrainment of the air into the powder bed and then dispersion (i.e. de-agglomeration) of the active drug particles to approach their primary particle size. Achieving efficient powder entrainment, and as a result close to complete device emptying, is important to ensure the delivery of a consistent therapeutic dose. De-agglomeration to a fine, respir-

able particle size, on the other hand, ensures that the drug is delivered to the target region of the respiratory tract, and that a suitable bioavailability is therefore achieved. For the majority of DPIs (which are passive devices) these twin goals must be achieved by controlling particle-particle interactions such that the inhalation effort of the patient provides sufficient energy via the airflows in the device for dispersion/aerosolisation processes to proceed to a clinically effective conclusion.

As air is drawn through a DPI by the patient, the powder bed is subjected to an aerodynamic drag force and an applied velocity gradient. These parameters influence the rate of acceleration of the particles, and the energy of impact collisions between particles and between particles and the device.[10] De-agglomeration may result from fractures caused by these collisions and from the more gradual process of erosion from the bed.[10] Increasing the flow velocity increases the pressure drop across,[6] and turbulent kinetic energy within,[10] the device, driving up the energy potentially available for dispersion.

Potential strategies to improve drug delivery include reducing the strength of particle-particle interactions [2] or increas-

ing the intensity of the dispersion process for higher energy impaction. One way to support research in this area is to look at the strength of individual particle-particle interactions, using, for example, atomic force microscopy (AFM) measurements. An alternative is to look at the behaviour of the powder bed in its entirety and its response to airflow rate: this latter approach is explored here.

INVESTIGATING DISPERSION AS A FUNCTION OF AIRFLOW RATE FOR MODEL DPI COMPOUNDS

Experiments were carried out to investigate the dispersion behaviour of two model compounds: Lactohale 300 (LH300) (DFE Pharma, Goch, Germany) and salbutamol sulphate (SS). The particle size of aerosols produced using a Rotahaler® (GSK, London, UK) commercial DPI were measured at airflows in the range 30-180 L/min using the Spraytec laser diffraction analyser (Malvern Instruments, Malvern UK). This upper limit is well above the maximum figure specified for DPI testing (100 L/min) within pharmacopoeia guidelines but reflects the peak inspiratory flow achieved by some patients with certain inhaler devices; the lower limit lies within the accepted range for routine testing. The samples were also measured as liquid dispersions in order to establish a primary particle size distribution against which the degree of dispersion achieved using the DPI could be benchmarked.

Figure 1 shows primary particle size distribution data for the two samples. No evidence of agglomerates was observed, and the Dv50 values for both compounds lie below 5 µm. These results set a baseline for optimal de-agglomeration, suggesting a maximum Fine Particle Fraction (FPF) of around 65% for the LH 300 and 75% for the SS.

The average particle size distributions reported for the SS formulation during dispersion using the Rotahaler at different flow rates are reported in Figure 2.

At low airflow rates, dispersion of the SS produces a monomodal particle size distribution with a Dv50 that falls from 85 µm at 30 L/min to around 19 µm at 60 L/min. However, at 60 L/min a shoulder appears at around 60 µm, suggesting the evolution of a second, smaller particle size mode within the distribution. A bimodal distribution is very much in evidence at all flow rates in the range 90-180 L/min, where the mode
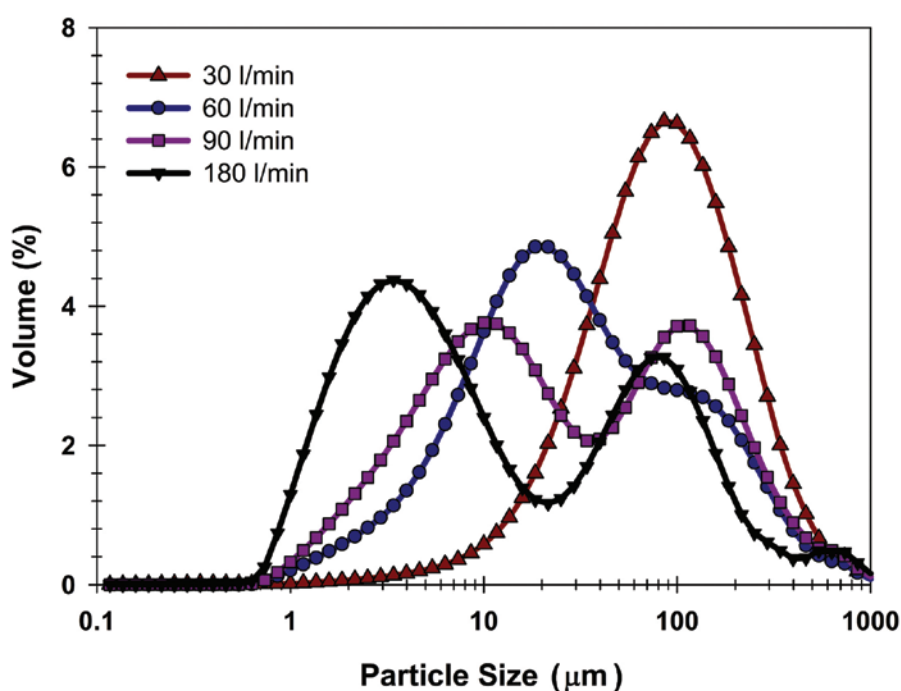

Figure 2: Particle size distributions for salbutamol sulphate measured at flow rates in the range 30-180 L/min.
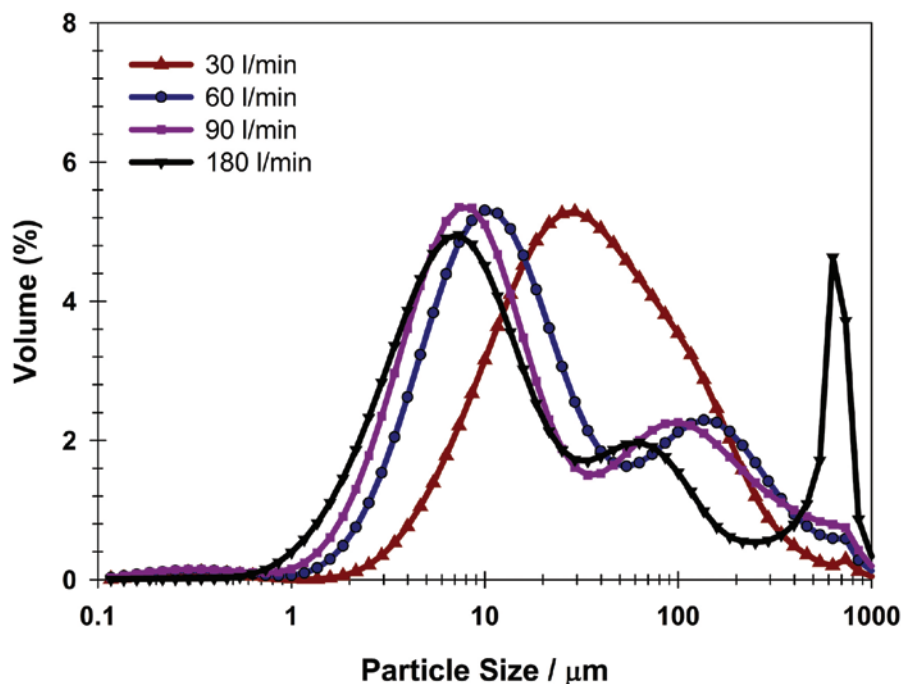
Figure 3: Particle size distributions for Lactohale 300 measured at flow rates in the range 30-180 L/min.

emitted dose is 63.4%. In contrast, LH300 exhibits a steadier rise, from a lower base point (23.7% at 30 L/min) to a much higher upper figure (81.9% at 90 L/min).

INTRODUCING THE RELATIVE DE-AGGLOMERATION VERSUS FLOW RATE PROFILE

The measured dispersion data can be displayed in a number of different ways. There are, however, obvious benefits in tracking how the FPF (defined as the sub-5.4 µm fraction in this case) changes as a function of flow rate, since this parameter is indicative of the amount of material likely to deposit in the lung. 5.4 µm was selected as the FPF cut-off diameter in this case, as this represented the upper boundary of the size band reported by Spraytec which included data at 5 µm. Normalisation of these results against the primary particle size data for each compound removes a confounding influence from this analysis. With the SS and LH300, 'perfect' de-agglomeration would yield different FPFS – around 75% and 65%, respectively – because these two formulations have different primary particle size distributions.

Comparing the proportion of the dose dispersed to below 5.4 µm with the baseline figure provided by the wet dispersion measurements yields 'relative de-agglomeration', which takes into account this difference. The relative de-agglomeration-flow rate

for the finer particle population is seen to shift towards smaller sizes as the applied flow rate increases. Furthermore, as flow rate increases, the area under the curve of the coarser particle population gradually decreases while that of the finer population increases, illustrating the continuing de-agglomeration.

The equivalent data for LH300 show quite different behaviour (see Figure 3). A monomodal distribution is observed at an airflow rate of 30 L/min but a well-defined bimodal distribution establishes at 45 L/min which persists at all higher flow rates. The finer population is centred on a particle diameter of around 7-8 µm at all flow rates, and the coarser population is similarly constant. The area under the fine and coarse parts of the bimodal curve are also, to a significant extent, flow rate independent. At very high flows there is evi-

dence of extremely coarse material exiting the device; this is attributed to the entrainment of solid plugs of undispersed powder.

Emitted dose data (expressed as a percentage of loaded dose) for both compounds (see Figure 4) provide complementary information, indicating the extent of powder entrainment, rather than dispersion. These results suggest that for SS little improvement in emitted dose is achieved by increasing flow rate above 60 L/min, at which point

Flow rate (L min⁻¹)	Salbutamol Sulphate	Lactohale 300
30	32.6 (15.4)	23.7 (10.5)
45	49.6 (15.1)	66.5 (6.4)
60	63.4 (4.6)	74.0 (2.7)
90	60.8 (4.8)	81.9 (2.5)
120	67.4 (5.4)	85.1 (2.2)
150	66.5 (7.8)	85.9 (4.9)
180	68.9 (5.9)	86.4 (1.4)

Figure 4: Emitted doses of processed salbutamol sulphate and Lactohale 300 (expressed as a percentage of loaded dose) dispersed from the Rotahaler® at different flow rates (L/min).
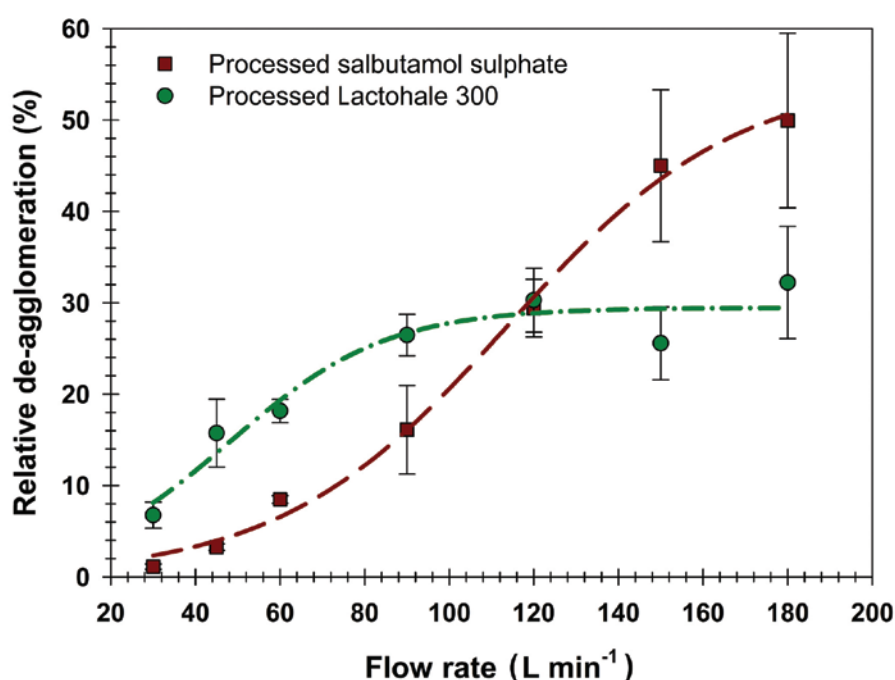

Figure 5: Relative de-agglomeration versus flow rate profiles for salbutamol sulphate and Lactohale 300, including empirical model curves.

	Maximum extent of de-agglomeration (*a*)	Change in de-agglomeration with flow rate (*b*)	Flow rate required to achieve 50% de-agglomeration (*X0*)
Salbutamol sulphate	54.92	26.94	113.77
Lactohale 300	29.48	18.6	48.01

Figure 6: Relative de-agglomeration profile parameters for salbutamol and Lactohale 300.

profile (see Figure 5) shows the progression of dispersion towards the ideal as the applied flow rate is increased.

The relative de-agglomeration profiles for SS and LH300 provide a graphical summary of the very different dispersion behaviour observed with SS and LH300. With SS, relative de-agglomeration rises steadily with flow rate to reach around 50% at 180 L/min. In sharp contrast, with LH300 the relative de-agglomeration value reaches a plateau of around 30% at a flow rate of 90 L/min. Beyond this, the degree of de-agglomeration achieved appears to be independent of flow rate.

Empirical modelling was carried out to represent the developed de-agglomeration profiles in terms of specific parameters. Performing a non-linear least squares regression produced a good fit using a three-parameter sigmoidal equation of the form (see Figure 5):

$$y = \frac{a}{1 + e^{-\left(\frac{x-x0}{b}\right)}}$$

Where parameters *a* and *b* are the maximum extent of de-agglomeration of the powder and the change in de-agglomeration with flow rate respectively, and χ0 is the flow rate required to achieve 50% de-agglomeration. Values of these parameters for SS and LH300 are shown in Figure 6.

RELATIVE DE-AGGLOMERATION PROFILES TO COMPARE DISPERSION PERFORMANCE

Values for the three parameters derived from the relative de-agglomeration profile efficiently characterise the unique dispersion behaviour of the different compounds. Taken together these data summarise the outcome of the complex interplay between the applied aerosolisation energy and the cohesive forces opposing dispersion. More practically, they provide valuable screening information for devising a formulation strategy for a particular drug.

The maximum extent of relative de-agglomeration is indicative of the optimal achievable performance within the flow field of the device, while the flow rate to achieve 50% relative de-agglomeration suggests how easy or difficult dispersion will be. The change in relative de-agglomeration with flow rate reflects the likely dependence of drug delivery on patient inhalation characteristics. These are all pertinent inputs to the decision-making process surrounding formulation development and its matching to a device system.

An ideal formulation for respiratory delivery would have a high maximum percentage de-agglomeration (*a*), a low change in de-agglomeration with flow rate value (*b*) and require a low flow rate to achieve 50% de-agglomeration (χ0). Such formulations might be expected to deliver a high proportion of the loaded dose successfully and consistently, even for physically weak patient groups.

In combination with the emitted dose and particle size distribution data, the relative de-agglomeration curve also supports a more detailed analysis of the possible mechanisms of entrainment and dispersion. With SS, increasing flow rate fails to increase emitted dose above a plateau of around 65%, reached at around 60 L/min. However, the relative de-agglomeration curve shows that flow rates in excess of this figure are beneficial in terms of dispersion. Although higher flow rates drive no more material from the device, they promote the dispersion of larger emitted agglomerates to a respirable size (Figure 5), and the continued dispersion of smaller particles (Figure 2).

Interestingly, even though the mode of the finer SS population shifts towards a smaller particle size with increasing flow rate, the size of the larger population remains constant. This suggests that break-up is not a step-wise process but rather that certain agglomerates in the 30 to 600 µm range break up almost completely while others remain intact. Reasons for this are still speculative, but one explanation could be that higher flow rates increase the incidence of impaction. If impaction-based dispersion results in a dramatic reduction in particle size then this would rationalise the observed behaviour.

With the LH300, a larger proportion of the dose is entrained (Figure 4), but the dispersion of this delivered dose plateaus at a low level (Figure 5). Neither result suggests any benefits to increasing flow rate above

BOX 1: LASER DIFFRACTION: REAL-TIME MEASUREMENT OF THE DPI AEROSOL

Uptake of the technique of laser diffraction by DPI researchers is largely attributable to the capability it offers for real-time particle size measurement of the emitted aerosol. With measurement rates in excess of 2.5 kHz, laser diffraction systems track changes in particle size which occur as a result of dispersion during a device actuation. Concentration is also measured as a function of time, making it a suitable technique for studying entrainment.

Particles illuminated in a collimated laser beam scatter light over a range of angles. Large particles generate a high scattering intensity at relatively narrow angles to the incident beam, while smaller particles produce a lower intensity signal but at much wider angles. Laser diffraction particle size analysers record the pattern of scattered light using an array of detectors and then calculate particle size distribution from this, for the entire sample, using an appropriate light scattering model.

The technique can be used to measure both wet and dry samples, including sprays from 0.1-2000 µm in size, comfortably covering the range of interest for DPIs; from primary particles through to agglomerates. Instruments configured for DPI analysis can be set up, in terms of test flow rate, in accordance with pharmacopoeia guidelines for aerodynamic particle size measurement by cascade impaction. However, since measurement is unaffected by airflow, results can also be gathered outside this range, a prerequisite for this study.

around 90 L/min, but ultimate performance is relatively limited in terms of the likely success of drug delivery, with only around 25% of the dose being delivered in a respirable form.

The data here suggest there are relatively weakly bound particulate structures within

Powders with a high value of *a*, and low values of both *b* and χ0 are superior in terms of drug delivery performance, dispersing easily and consistently to a high respirable fraction.

Deriving these parameters from the relative de-agglomeration profile is consequently a

> "In combination with the emitted dose and particle size distribution data, the relative de-agglomeration curve also supports a more detailed analysis of the possible mechanisms of entrainment and dispersion"

the powder bed that are easily detached, but that these are present alongside strongly bound agglomerates that cannot be dispersed even when the available dispersion energy is high (high flow rates).

IN CONCLUSION

The relative de-agglomeration *versus* flow rate profile provides a tool for contrasting and comparing the performance of DPI formulations in a given device. Derived from laser diffraction measurements of dispersed particle size at flow rates across and beyond the range routinely adopted for DPI characterisation, it quantifies and summarises the dispersive behaviour of a formulation dose. Empirical modelling indicates that the shape of the de-agglomeration profile can be understood using three parameters:

- Maximum extent of de-agglomeration of the powder (*a*)
- Change in de-agglomeration with flow rate (*b*)
- Flow rate required to achieve 50% de-agglomeration (χ0)

powerful way of characterising the behaviour of the powder bed in a way that will reflect in-use performance. The approach allows researchers to screen new powder/device combinations rapidly and to summarise dose performance in an efficient and informative way, supporting the swifter development of more successful DPI solutions.

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DRUG DELIVERY TO THE LUNGS (DDL) 25
Edinburgh, Scotland, December 10-12, 2014

In 2014 we celebrated 25 years of Drug Delivery to the Lungs with record-breaking delegate numbers and sell-out Exhibition Hall.

Keynote speaker Professor Peter Stewart, Monash University, Australia, presented the DDL Lecture on, "Inhaled Drug Formulation - the Past, Present & Future of Powders for Inhalation". This was very well received by a packed auditorium and reflected the theme of looking back over the past 25 years of drug delivery and anticipating where drug delivery will be in 2039!

Keynote speaker Prof Peter Stewart, Monash University, Australia, presented the 2014 DDL Lecture.

Each year we present a "What on Earth" session, which provides the opportunity for unusual lectures to be given. For DDL25 we welcomed Bath and England rugby legend John Hall, who spoke about his race 3,000 miles across North America in support of Asthma UK. This presentation was not only exceptional but was also a real tear jerker.

We hosted a spectacular Celebration Jubilee Dinner at the Conference Centre with over 500 guests attending. Father Christmas hosted our drinks reception and we were then entertained by a Frank Sinatra Tribute Act, a Rabbie Burns Actor and the bagpiping, fiddle playing PeatBog Faeries who got everybody up and dancing.

The 2014 conference provided the opportunity for companies to exhibit in the new purpose built exhibition hall at the Edinburgh International Conference Centre (EICC). In excess of 80 exhibitors attended taking advantage of our varied sponsorship packages, including our Platinum Sponsors 3M Drug Delivery Systems, Cascade Technologies Ltd, and Intertek Melbourn.

PREVIEW OF DDL26

The next Drug Delivery to the Lungs Conference, DDL26, will once again be held at the EICC from Wednesday 9th to Friday 11th December, 2015. Edinburgh is an excellent location for DDL as it is easily accessible for delegates from Europe, the UK and the wider world as well as being a beautiful historic city, which looks particularly festive in December.

DDL provides an annual forum for scientists, academics, clinicians, regulatory and industry specialists involved in developing medicines for inhalation.

DDL26 will have five themed sessions each with a combination of invited and submitted lectures given by experts in the field of inhalation and students working to advance respiratory science.

Topics to be covered at DDL26 include:
- Devices and technology
- Advances in formulation and analytical science
- Nasal, buccal and upper airways delivery
- Delivery of biomolecules, future challenges
- Impact of disease on lung physiology and implications for drug development
- Pharmaceutical development – from molecule to patient
- Innovation in formulation – what can we learn from other industries?

You are invited to submit an abstract for selection as either a poster or podium presentation relating to the above Themes by Friday July 26, 2015.

For submission details please visit our website: www.ddl-conference.org.uk.

DDL is dedicated to supporting junior researchers and at DDL each year we invite abstract submissions for The Pat Burnell New Investigator Award. Pat was a key instigator in setting up the DDL conference over 20 years ago. Her vision was for a conference that is accessible and inclusive to all. She was passionate about aerosol science and in her own words: "Those who do the research should present their work, not their stuffy old boss or academic supervisor".

This award recognises Pat's vision for the conference and has been designed to

DDL25 Pat Burnell Award Winner, Abhinav Kumar, King's College London.

encourage junior researchers to present their work at DDL. It will be awarded to the best research from either academia or industry, from a new researcher.

To find out more about the award and to apply, please visit the website.

A selection of sponsorship opportunities are available for companies who would like to promote their services at DDL26.

For 2015 we are excited to introduce a new level of sponsorship targeted at those companies who wish to send five or more delegates to the conference and want to experience some of the sponsorship promotional benefits without having an exhibition stand. In line with our charter to provide networking, development and training for inhalation scientists each "training" sponsorship also includes additional tickets for recent graduates or academic collaborators.

Please note that exhibition spaces are limited, and are on a first-come-first-served basis. To view all sponsorship options please visit our website.

The DDL26 Conference attracts world-class pharmaceutical business leaders and academics. Join us for this prestigious event and book your place on-line now by visiting our website: **www.ddl-conference.org.uk**

DDL26
drug delivery to the lungs 26

EDINBURGH INTERNATIONAL CONFERENCE CENTRE
Wednesday 9th – Friday 11th December 2015

Drug Delivery to the Lungs is Europe's premier conference and exhibition dedicated to pulmonary and nasal drug delivery

- *DDL* provides an annual forum for scientists, academics, clinicians, regulatory and industry specialists involved in developing medicines for inhalation.

- *DDL* attracts a diverse and extensive selection of posters, presentations. Our Exhibition attracts the leading players from the Pharmaceutical Industry, Suppliers, Instrument Manufacturers and Contract Research Organisations.

About the Conference Programme

DDL26 will have 5 themed sessions each with a combination of invited and submitted lectures given by experts in the field of inhalation and students working to advance respiratory science.

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- Delivery of Biomolecules, future challenges
- Impact of disease on lung physiology and implications for drug development
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About the Exhibition

The 2015 Conference provides the opportunity for companies to exhibit in the new purpose built Exhibition Hall at the EICC. Last year in excess of 80 exhibitors attended taking advantage of our varied sponsorship package including our platinum sponsors **3M Drug Delivery Systems, Cascade Technologies Ltd and Intertek Melbourn.**

As an exhibitor, a much wider impact is made by linking you with over 500 delegates from the UK, Europe and the wider World giving you an opportunity to meet with all the key players involved in developing medicines for inhalation.
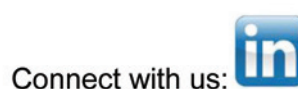
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PRODUCTION TECHNOLOGY

PROFITABLE ASSEMBLY AUTOMATION
THROUGH USE OF STANDARDISED MACHINE PLATFORMS

Here, Reiner Zeidler, Sales Manager, Medical Systems, teamtechnik Group, describes the company's modular TEAMED production system, and how it meets the inhaler device industry's needs – from early development applications right through to commercial-scale manufacture.

There is increasing demand for new solutions to automate the manufacturing of inhaler devices from Phase I clinical trials through to a successful high-volume pro-

> "The TEAMED platform incorporates processes from prototype production directly into series manufacturing, thus verifying critical process steps at the earliest possible stage"

duction program. Teamtechnik Group is a leading player in the development and implementation of turnkey production systems for medical devices, offering a wide range of machine platforms.

WHY USE MACHINE PLATFORMS?

With its TEAMED platform system (Figure 1), teamtechnik offers a scalable linear production system, consisting of proven standard modules which are then tailored specifically for each customer. Using such tested modules, the engineering required is much reduced and so are, therefore, machine delivery times.

The TEAMED platform enables the integration of sophisticated assembly processes

(Figure 2) with up to 100% end-of-line testing. It also facilitates production which is compliant with global standards – such as cGMP, US FDA and CE – and is certified to Class 6 Clean Room specifications. The TEAMED platform incorporates processes from prototype production directly into series manufacturing, thus verifying critical process steps at the earliest possible stage, providing reassurance for future series production from the outset.

The TEAMED platform has been developed for proof of principle applications as well as for high-speed industrialisation. Drawing upon teamtechnik's comprehensive library of processes, the TEAMED solution optimises assembly processes and reduces time to commercialisation for new products.

A typical device project development and commercialisation cycle for a new device, utilising the TEAMED platform, is described below.

"TEAMED POP" FOR PROTOTYPE PRODUCTION

Phase I Clinical Trials
Assembly of injection devices involves many complicated processes, which must either be monitored in-process, or results must be verified after the process. In an ideal scenario, in

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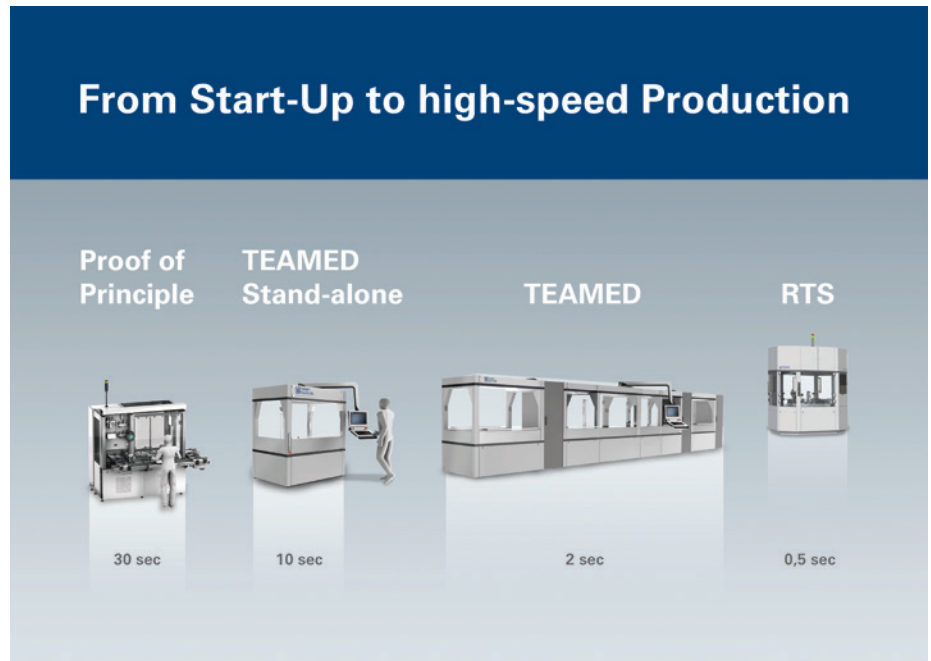D-71691 Freiberg am Neckar
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Figure 1: Modular platforms for assembly and functional testing.

Figure 2: Assembly system at TEAMED platform.

Figure 3: Blister coiling.

order to minimise time to market, a device design and assembly process would be completely defined from the outset of Phase I. For reasons of cost, risk and design evolution, this ideal is not generally possible and teamtechnik's TEAMED PoP (Proof of Principle) platform provides a solution for such a challenge.

Incorporating both automated and manual elements, TEAMED PoP offers the ability to perform and monitor critical assembly processes with automatic solutions at a very early stage in a project, whether or not a device design has been fully defined at that point. Able to accommodate up to five process operators working at the machine, it is often the case that a customer will engage with teamtechnik and utilise TEAMED PoP, while a device is still under development.

"Able to accommodate up to five process operators working at the machine, it is often the case that a customer will engage with teamtechnik and utilise TEAMED PoP, while a device is still under development"

Figure 4: teamtechnik's cam driven machine, RTS.

Figure 5: teamtechnik provides resident engineers, based locally and available onsite, during post-installation and ramp-up phase.

TEAMED "STAND-ALONE" FOR SMALL-VOLUME PRODUCTION

Phase III Clinical Trials

Providing continuity from the Phase I experience utilising TEAMED PoP, the same process units can then be integrated into a TEAMED Stand-Alone machine for small-volume production to support Phase III trials.

TEAMED Stand-Alone is a semi-automated assembly line with process materials being fed by operators, and with process stations being linked by a carrier transport system. The carrier features have the same design as in the corresponding TEAMED PoP machine, although typically incorporating additional nests for manually pre-loaded parts. Although most of the assembly operations will be performed automatically, the refined process stations are based on similar technologies to those on the precursor TEAMED PoP system.

"TEAMED" PLATFORM FOR INDUSTRIALISATION

Commercial Scale

For high-volume, commercial scale production, teamtechnik provides a fully-automated TEAMED line with all device components being delivered by bowl feeders or palletising systems. The carrier design is ideally based on the same concept as used for the earlier TEAMED PoP and TEAMED Stand-Alone machines.

A number of critical processes, such as dosing, blister coiling (Figure 3) or welding (ultrasonic or laser) – will typically have been refined and validated with the TEAMED PoP and TEAMED Stand-Alone

systems, and are continued through in the design of the high volume manufacturing line. The simple replication of validated processes can significantly reduce time to market for a new device, thereby improving return on investment. This benefit can be realised by the modular design of the TEAMED system, using individually customised processes and a machine concept which combines the flexibility and operational efficiency of pre-validated servo-actuated motions and cam-driven units.

"RTS" CAM-DRIVEN PLATFORM FOR HIGH SPEED PRODUCTION

teamtechnik's cam driven machine "RTS" (Figure 4) represents the company's high-speed automation platform. Typically operating at up to 120 cycles per minute, RTS offers a ring transfer system, providing between eight and 32 individual stations, and is designed for processes which require higher outputs.

MARKET LEADERS TRUST TEAMTECHNIK

Customers rightly expect robust, reliable and cost-effective production systems for their medical device products. Providing the foundation for long-lasting customer relationships, teamtechnik's engineers are

well-versed in the design and building of process technologies which offer sophisticated assembly and functional testing for a wide range of production applications.

GLOBAL SERVICE CAPABILITY

Based in Freiberg, Germany, teamtechnik Group is an international leader in highly flexible automation technology – providing intelligent and reliable automation solutions for medical, pharmaceutical, diagnostic and other industries for several decades.

With 900 employees throughout the world, generating annual revenues of over €150 million (£108 million), teamtechnik supports customers from sites in Germany, Poland, France, China, Korea and the US.

To ensure customers have access to relevant expertise during the post-installation and ramp-up phase of their projects, teamtechnik also provides resident engineers - based locally and available on-site

- during this critical phase of a program (Figure 5). Through its global service network, teamtechnik also ensures that production equipment is available around the clock, providing customers with dedicated service team contacts, each with comprehensive knowledge of a particular customer's manufacturing system.

"The simple replication of validated processes can significantly reduce time to market for a new device, thereby improving return on investment"

Phillips Medisize

Partnerships Built on Innovation

HUMAN-CENTRED DESIGN
AT THE HEART OF A SUCCESSFUL PRODUCT DEVELOPMENT PROCESS

In this article, Bill Welch, Chief Technology Officer, and Jeremy Odegard, Design & Development Center, both of Phillips-Medisize, provide an insight into how the company's human centred design approach fits into its integrated product development process.

During the development phases, pharma and medical device companies can encounter obstacles complying with the US FDA's drug and medical device regulations, as well as other global regulations that determine which current good manufacturing practices (cGMPs) and quality system regulations apply for product manufacturing. There is also the need to manage complicated supply chain logistics from design, testing and development to low-volume clinical trial manufacturing as well as the scale-up to higher-volume commercial production. The most minor detail can derail the development of a successful product, resulting in lost time and resources and deadlines missed. This could cause product development or regulatory submission to stall before it ever reaches the market.

Project complications and delays can arise as a result of collaboration among disparate organisations. For example, a design firm might not understand what can be achieved in injection moulding processes.
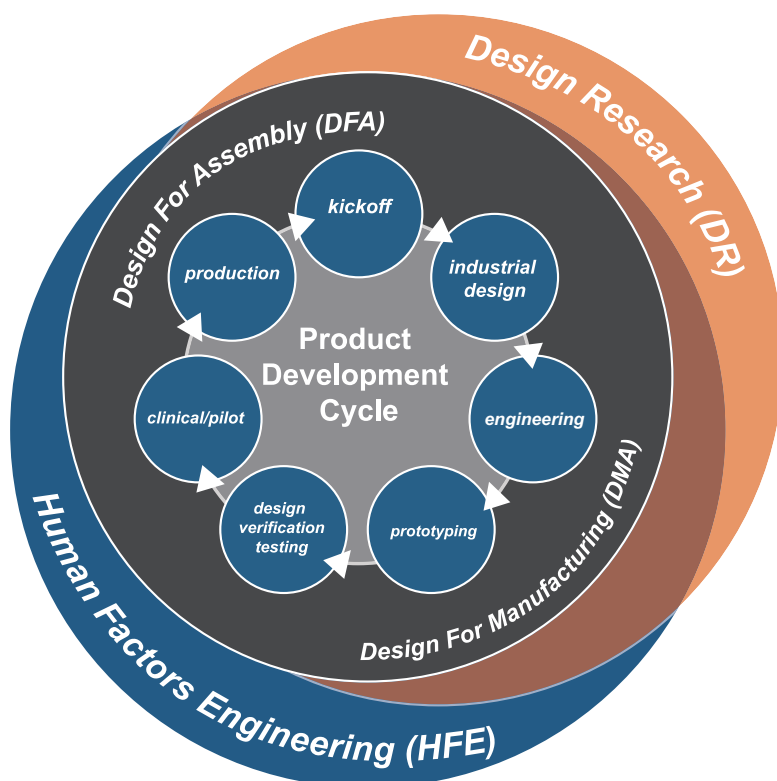

Figure 1: Phillips-Medisize's integrated product development cycle.

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Further, designs may not be optimised for manufacturing or assembly. By applying adequate due diligence in choosing the right partner, pharmaceutical or biotechnology and medical companies can improve the odds of launching a successful new drug product into the marketplace – on time, and on budget.

INTEGRATED PRODUCT DEVELOPMENT

Phillips-Medisize's integrated product development process combines human-centred design principles with a solid design for manufacturing (DFM) and design for assembly (DFA) philosophy. It addresses design research, industrial design and human factors engineering (HFE) focusing on product usefulness, usability, desirability and manufacturability (see Figure 1).

The key benefits of this are product adoption and compliance; predictable processing; overall product quality improvement; cycle time reduction and stakeholder satisfaction.

The human-centered approach is not limited to a single phase nor is it a standalone module that can simply be attached to the front-end of a program. It needs to be embedded into the cultural fabric of an organisation in order to be effective.

HUMAN-CENTRED DESIGN PRINCIPLES

Design Research

Design research activities are typically conducted at the front end of a development cycle in order to establish a firm foundation for future design work (Figure 2). This is required to determine the needs of end users, uncovering attributes that will resonate with them on an emotional level. Common design research methods include targeted interviews, contextual observation (for example, witnessing a surgical procedure in an operating room, or shadowing a diabetic patient through their daily testing and insulin injection routine in the home), participatory workshops, analogous product benchmarking, and trend tracking. These processes allow a cross-functional development team to appreciate circumstances, environmental conditions, and user expectations in an effort to identify design opportunities. Discoveries made through design research inform the development process, improving the likelihood of success upon market introduction.
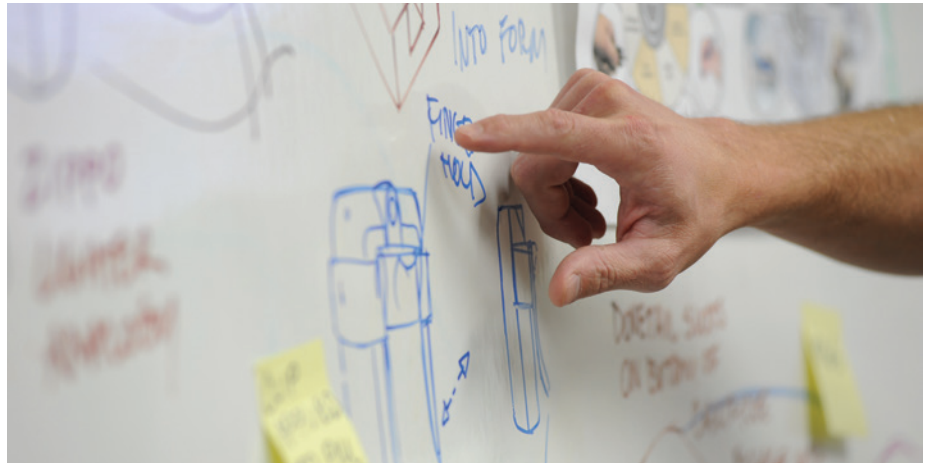

Figure 2: Design research is typically conducted at the front end of a development cycle in order to establish a firm foundation for future design work.

Industrial Design

Industrial designers build upon the foundation of design research, translating discoveries, product performance goals and marketing objectives into tangible concept directions. Product form, user interface, ergonomics, aesthetic detail treatment, material selection, and manufacturing approaches are all considered during this phase which typically begins with collaborative brainstorming from multiple professional disciplines. Industrial designers then narrow their focus to a manageable set of concepts that may be evaluated through illustrations, preliminary CAD models, and physical prototypes.

Human Factors Engineering

The objective of HFE is to minimise use-related risks and ultimately to ensure safe and effective use. HFE activities may include product handling studies, usability testing with representative users, and final verification/validation studies to satisfy regulatory expectations. HFE methods are applied throughout the development cycle to mitigate product related safety risks and justify design decisions.

HFE starts early in a design cycle and should be an integral part of the development process. Design inputs such as user profiles, use environment, and other contextual influences must be considered as early as possible. Proper planning, execution and documentation of HFE activities throughout the development process should streamline the submission process for regulatory approval.

A focused Human-Centered Design approach promotes intuitive, usable, and desirable devices (Figure 3).

"Almost all of the extremely diverse medical sectors use and benefit from our HCD approach, among them diabetes, ophthalmology, oncology, gynecology, cardio-vascular surgical intervention. In the field of medical devices, we are involved in the development of 'knock-your-socks-off' technologies and applications – developed all the time – for ever more complex Class III devices, those still requiring pre-market approval. Class III devices are usually those that support or sustain human life," said Phillips-Medisize Chief Technology Officer Bill Welch.

DFM AND DFA

Design for manufacturing (DFM) and design for assembly (DFA) are also foundational elements of a robust product development process. Much like human-centred design principles, a sound DFM/DFA philosophy should be a cultural mindset, becoming ingrained in

USABLE:
- Proven minimised risk of use error
- Comfortably achievable user input forces
- Accommodation of user group abilities / limitations

INTUITIVE:
- Predictable device behaviour
- Simple operating sequence
- Alignment with mental models
- Simple user actions / motions
- Meaningful form language

DESIRABLE:
- Fitting into the lifestyle of the intended user
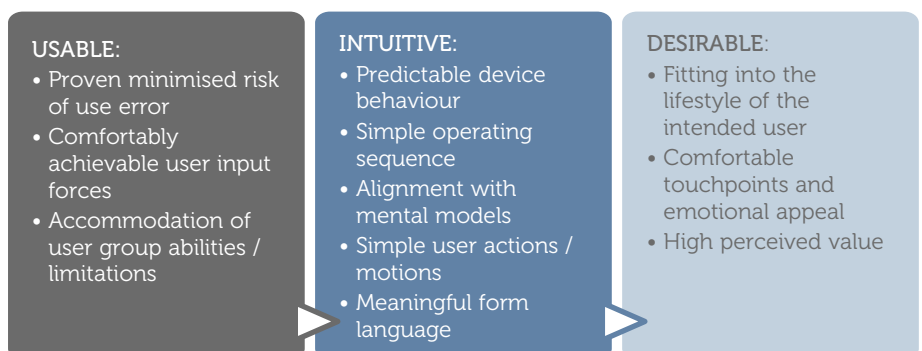- Comfortable touchpoints and emotional appeal
- High perceived value

Figure 3: Summary of criteria for achieving usable, intuitive desirable device design.

all phases of development. While HFE evaluation throughout the process is typically focused on the user's experience, DFM and DFA are focused on manufacturing quality, cost and risk. Certain aspects of DFM, such as design guidelines for moulded plastic or metal parts, have proven manufacturing process principles behind them and applying just a handful of established DFM guidelines for moulded parts can prevent a majority of design issues.

The same can be said for DFA, in which planning for manual, semi-automated, or automated assembly from the early stages can prevent issues that would otherwise be found during clinical, pilot, or manufacturing launch builds when mitigation of issues becomes much more costly. Designers, engineers and manufacturing representatives must collaborate early and often to develop designs that meet targeted quality and cost objectives, and other established program goals.

DFM AS A GUIDING PHILOSOPHY

Successful DFM requires a culture that unites product development and manufacturing and appreciates early manufacturing involvement from the concept phase. Since most of the product cost (as well as quality and risk) are driven by decisions early in the design cycle, the product development team must include expertise in DFM for the intended manufacturing processes. In the spirit of innovation and creating improved patient outcomes at a lower cost, it is recognised that DFM guidelines must sometimes be challenged. In these cases, the product development team must be committed to risk mitigation by applying computer aided engineering (CAE) tools such as mouldflow, finite element analysis (FEA), and tolerance analysis to an unfinished design, and subsequent prototyping to verify the CAE output.

In the case of injection moulded plastic components, the design team understands that part design dictates mould design and can envision how steel is wrapped around part geometry to create tooling capable of meeting the required volumes and quality requirements when in production. From a development standpoint, both the mould geometry and injection moulding process must align with the part requirements, mould construction, and moulding process.

Finally, the culture must support the belief that DFM must be applied across the product development process by a fully engaged multidisciplinary team including manufacturing representatives. DFM cannot be viewed simply as a checklist to be completed or a task in the development cycle. Early manufacturing involvement not only brings DFM expertise to the product development team, it also promotes concurrent early learning and buy-in by the manufacturing team, reducing lead time and risk downstream.

COST-DRIVEN SOLUTIONS

Many customers are interested in getting their ideas transformed into a functional product, relying on the expertise of the Phillips-Medisize Design Development Center (DDC) to handle all the industry-critical factors in the shortest possible time. The company has developed an own-product development process to provide time and cost optimised procedures, allowing it to develop the simplest devices to highly complex systems.

Based on an article that appeared in Medical Plastics News, Issue 23, p 14.

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IMPROVING THE REALISM AND RELEVANCE OF MOUTH-THROAT MODELS FOR INHALED PRODUCT TESTING

In this piece, Mark Copley, Sales Director of Copley Scientific, provides some background on mouth-throat models for OIP testing, and puts forward experimental evidence to suggest that Alberta Idealized Throats represent actual deposition behaviour more closely than the USP / Ph Eur induction port.

Last year's announcement of US FDA funding to support the experimental assessment of different mouth-throat models for orally inhaled product (OIP) testing [1] draws attention to the recognised limitations of the standard US and EU Pharmacopoeias (USP/Ph Eur) induction port used for cascade impaction (CI) measurements.

Primarily developed to meet requirements for a robust and simple test set-up for quality control (QC), this standard interface is a uniform right angled bend that fails to provide an accurate *in vitro* realisation of flow through the upper respiratory tract.[2] This limitation is becoming increasingly important as the industry works towards better *in vitro-in vivo* relationships (IVIVRs) to support product development. During OIP development, better IVIVRs aid the faster commercialisation of efficacious products and the more secure demonstration of bioequivalence, in the case of generics.

The Alberta Idealized Throats (see Figure 1), adult and child (AIT and C-AIT respectively), were developed specifically to meet the need to simulate dose deposition behaviour in the mouth-throat more closely during OIP testing. This article presents experimental work demonstrating the performance of these accessories relative to the USP/Ph Eur induction port. The results indicate that the AIT and C-AIT deliver data that are more representative of measured deposition behaviour, suggesting that they have a role to play in improving IVIVRs. The article concludes with a survey of other strategies that are also helpful in securing more representative testing.

EVOLVING REQUIREMENTS FOR OIP TESTING

Generally speaking, OIP testing is applied either:
• in QC – to verify that a product meets a defined specification ahead of batch release
• in R&D – to understand product behaviour better and optimise performance to deliver targeted *in vivo* drug deposition.
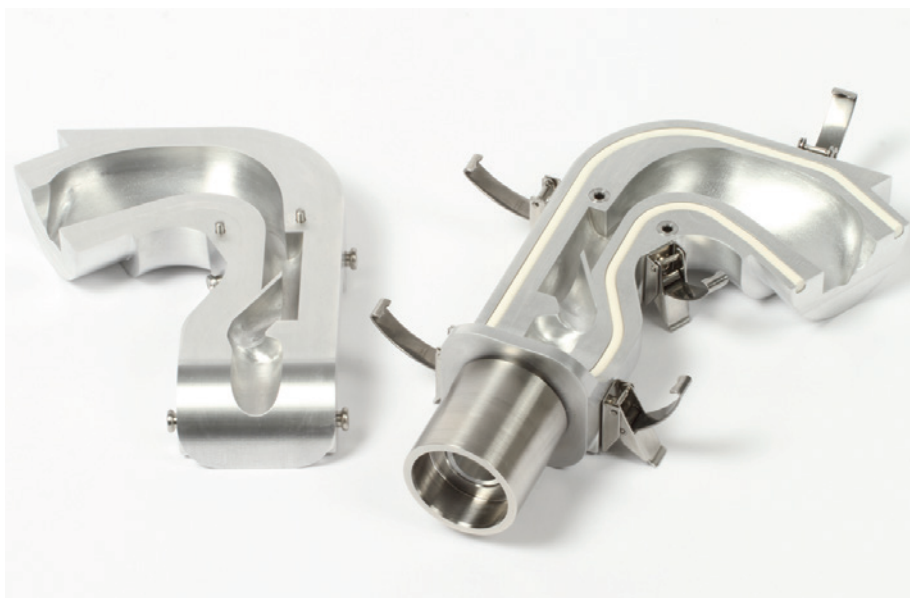

Figure 1: The AIT has a standardised, highly reproducible, human-like geometry offering robust performance across a broad range of flow rates.

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These two applications place different demands on an analytical test methodology. In QC the primary need is for simplicity, speed and sensitivity, since the goal is efficiently to assess samples against a specification. In contrast, during product development, the focus is on information gathering, to understand how to control product attributes to achieve the desired *in vivo* performance. Here accuracy and sensitivity alone do not guarantee success. Rather there is an additional need for the measured results to reflect *in vivo* performance and clinical efficacy, as far as possible.

The introduction of Quality by Design (QbD) brings this issue into sharper focus since a QbD approach is based on the knowledge-led manipulation of product parameters to deliver a defined Quality Target Product Profile (QTPP). To be useful within this context it is highly desirable that the results delivered by an in vitro method are closely representative of *in vivo* behaviour.

The particle size of aerosols emitted from an OIP directly influences deposition behaviour in the lung and is therefore a Critical Quality Attribute (CQA). CI testing is the primary particle sizing method used, principally because it measures the aerodynamic particle size distribution (APSD) of the active pharmaceutical ingredient (API) within a formulation, for the *entire* (collected) delivered dose. These features give the resulting data a high degree of relevance. Measurements are typically carried out using either an Andersen Cascade Impactor (ACI) or Next Generation Impactor (NGI), with the USP/Ph Eur induction port acting as the inlet to the impactor, to which the OIP is interfaced through the use of a suitable mouthpiece adapter.

The design intent of the induction port was to provide a uniform and robust representation of the human throat for QC testing. The accessory fulfils this purpose since it is easy to use and its simple geometry allows reproducible and repetitive drug recovery. However, the induction port is known to capture less of the delivered dose than would be deposited in the mouth-throat during routine OIP use by a patient.[3,4] Though this limitation does not compromise QC testing it is a contributing factor to the poor IVIVRs that impact the relevance of testing in product development.

It should also be recognised that whilst a cascade impactor is not a lung model, and should not be considered as such, there is significant value in ensuring that the aerosol entering the cascade impactor is at least representative of the aerosol that enters the lungs, for the purposes of accurately measuring the APSD of the lung dose.

ALTERNATIVES TO THE STANDARD USP/PH EUR INDUCTION PORT

One fairly obvious alternative is a human throat cast.

A human throat cast provides a highly accurate representation of the mouth and throat, but unfortunately only for a single human subject. Because there are significant inter-subject differences in the geometry of the mouth and throat the use of different throat casts introduces an additional and substantial source of variability during testing. Furthermore there are a number of practical issues associated with the use of throat casts:

- their geometry is complex making them difficult to define dimensionally and manufacture reproducibly
- plastic-based materials typically used in their construction are prone to static, have poor durability and may release chemical extractables during analysis
- they are difficult to access internally for the purposes of drug recovery and dimensional verification
- they can be difficult to interface reliably with CIs.

In summary then, human throat casts offer representative testing for a very closely defined patient group, but at the expense of practicality, while the standard USP/Ph Eur induction port offers practicality but is poorly representative of *in vivo* behaviour. The AIT is a rigorously researched alternative to these options, designed to combine the advantages of both.

The geometry of the AIT is the product of more than a decade of research at the Aerosol Research Laboratory of Alberta (University of Alberta, Canada) and was developed using an extensive database of computed tomography (CT) scans and reviews of anatomical texts.

Today the AIT is a commercial product, precision manufactured to extremely close tolerances and designed to interface with a wide range of cascade impactors. Manufactured in metal it has a highly reproducible, human-like geometry which delivers performance that is validated against clinical data across a broad range of flow rates.[3,4,5] Following successful trials with the adult AIT [3,4,6] a child version has recently been introduced, to enable the more representative testing of products for paediatric use. The geometry of this accessory is based on CT upper airway data from nine children aged six to fourteen years.[7]

The following experimental studies demonstrate the performance of the AIT/C-AIT, contrasting it with that of a standard USP/Ph Eur induction port, and show how these accessories provide more accurate information for OIP development.

CASE STUDY 1: A COMPARATIVE TRIAL OF THE AIT AND USP/PH EUR INDUCTION PORT

To compare the performance of the AIT with that of the USP/Ph Eur induction port, APSD measurements were made for two different commercially available inhaler formats: a pMDI (active ingredient salbutamol sulphate(SS)) and a DPI (active ingredient formoterol fumarate).[6]

Full resolution CI measurements were made using an NGI, equipped with either the AIT or USP/Ph Eur induction port. In accordance with pharmacopoeial test specifications the pMDI was tested at a flow rate of 30 L/min and the DPI at a test flow rate of 60 L/min. All stages of the NGI and the AIT were coated with silicone oil applied in n-hexane solution (1wt%/v), for all measurements, but the USP/Ph Eur induction port was left uncoated, in line with standard practice. A pre-separator was incorporated between the inlet (AIT or induction port) and CI for DPI testing.

Each measurement was conducted six times, resulting in 24 separate APSDs. The results are summarised in Figure 2 which includes averaged profiles for distribution of the API (mean ±1 SD) across the collection plates of the CI, and in the throat and inhaler mouthpiece. These data were used to generate the standard particle size metrics used to characterise OIPs which include:

- fine particle dose (FPD) – the amount of drug which would be expected to reach the deep lungs on the basis of aerodynamic particle size (mg or µg)
- fine particle fraction (FPF) – the fraction of the delivered dose that would be expected to reach the deep lungs on the basis of aerodynamic particle size (%)
- mass median aerodynamic diameter (MMAD) – the particle aerodynamic diameter below which 50% of the particle population lies, on the basis of drug mass (µm)
- geometric standard deviation (GSD) – a measure of the breadth of the generated APSD.

Stage	USP/Ph Eur Induction Port		AIT		Stage	USP/Ph Eur Induction Port		AIT	
	Mean	SD	Mean	SD		Mean	SD	Mean	SD
T/MP	54.2	1.6	66.8	5.1	T/MP	1.4	0.2	3.2	0.2
1	2.9	0.6	1.1	0.2	Preseparator	4.3	0.2	3.4	0.2
2	1.8	0.1	0.7	0.1	1	0.7	0.1	0.3	0.0
3	4.0	0.3	2.2	0.6	2	1.0	0.1	0.7	0.0
4	16.0	1.9	12.7	2.0	3	1.2	0.1	1.1	0.1
5	14.2	1.5	15.5	0.9	4	1.1	0.1	1.0	0.0
6	38.0	0.6	4.3	0.5	5	0.4	0.0	0.4	0.0
7	0.7	0.2	0.7	0.1	6	0.1	0.1	0.1	0.0
MOC	0.5	0.1	0.5	0.1	7	0.1	0.0	0.1	0.1
					MOC	0.0	0.0	0.0	0.0
TOTAL	98.0	3.6	104.4	8.4	TOTAL	10.2	0.3	10.4	0.3
FPD	37.3	2.6	34.8	3.3	FPD	3.2	0.1	3.0	0.2
FPF	38.0	1.4	33.4	1.3	FPF	31.0	0.8	28.4	1.3
GSD	1.9	0.2	1.6	0.0	GSD	2.2	0.1	1.9	0.0
MMAD	2.5	0.1	2.2	0.1	MMAD	3.5	0.1	3.1	0.0

Figure 2: Summary data for the pMDI (left) and the DPI (right) for the USP induction port and AIT. T/MP = throat/mouthpiece. Values are reported as µg/actuation, and the derived metrics are based on total emitted mass/actuation from the inhaler. MMAD is reported in µm.

An upper size limit of 5 µm was used for the calculation of FPD and FPF, which were based on the total dose emitted by the OIP into the inlet. All calculations were carried out using CITDAS V3.10 software (Copley Scientific, UK), assuming the APSD to be uni-modal and log-normal.

The results show that for both inhalers the AIT captures more of the emitted dose than the USP/Ph Eur induction port, thereby reducing the mass of drug entering the NGI. This observation echoes those reported previously for the AIT,[3, 8] verifying its performance and potential value.

Furthermore, based on a previous study in which both the USP/Ph Eur induction port and the AIT internal geometry were coated,[3, 4] this improved performance can be safely attributed to the geometry of the AIT rather than the applied coating.

Figure 3 shows the data as cumulative APSDs based on NGI-sized mass. The NGI-sized mass is considered to be the portion of the dose that exits the induction port or throat and deposits on stages (and final filter) of the CI, having a particle size upper-boundary defined by the cut-off diameter of the preceding stage. This normally results in omitting the drug mass collected on the first stage of the impactor.

These plots show that the effect of the AIT extends beyond simply the amount of dose captured. For the pMDI, use of the AIT shifts the APSD to finer sizes across the entire sized range, a trend summarised by an observed increase in FPF of approximately 8%, when only considering the impactor-sized mass. The associated reduction in MMAD is 2.5 ± 0.1 µm to 2.2 ± 0.1 µm and there is also an observable narrowing of the GSD from 1.9 ± 0.2 to 1.6 ± 0.0. Similar observations have also been reported elsewhere.[9]

The same trends are observed with the DPI. Here the increase in FPF, based on impactor-sized mass alone, is approximately 10% and there is an associated decrease in MMAD from 3.5 ± 0.1 µm to 3.1 ± 0.1 µm. GSD narrows from 2.2 ± 0.1 to 1.9 ± 0.0.

In summary, the AIT collects more of the emitted dose than the USP/Ph Eur induction port, which is known to underestimate mouth-throat deposition, suggesting that the AIT produces more representative data. However, the results also suggest that the AIT does not retain all particle sizes to an equal extent, but rather has a greater influence on the larger particles emitted by either inhaler.

CASE STUDY 2: ASSESSING THE PERFORMANCE OF THE C-AIT

In a second experimental study the performance of the C-AIT was compared with
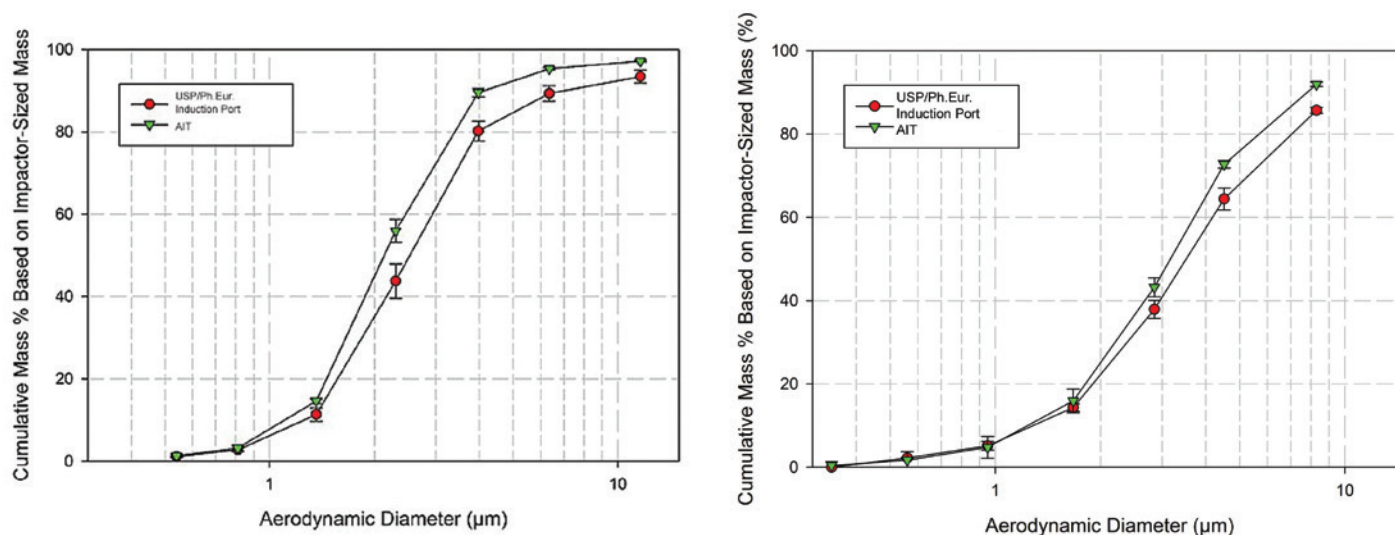
Figure 3: Cumulative aerodynamic particle size data for the pMDI and DPI based on impactor sized mass for the USP/Ph Eur induction port and AIT.
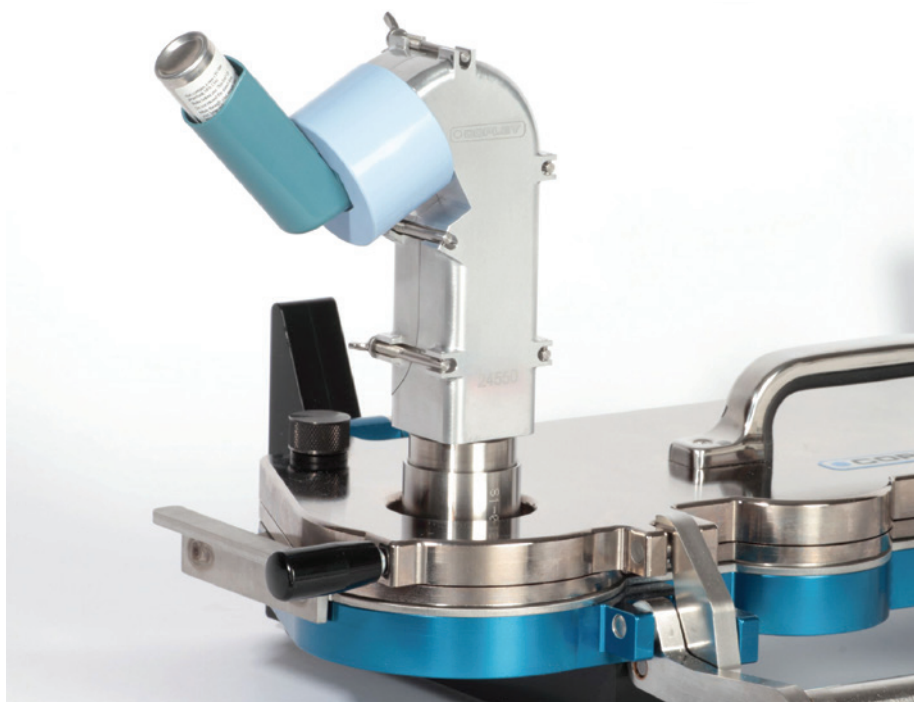
Figure 4: Test set-up for evaluation of the performance of the C-AIT showing NGI, C-AIT and pMDI.

Test	Device	Analyst	
		USP/Ph Eur Induction Port	C-AIT
1 2 3	Device 1	Analyst 1	Analyst 2
4 5 6	Device 2	Analyst 2	Analyst 1

Figure 5: Test programme for comparative testing of the C-AIT and USP/Ph Eur induction port which involved two devices and two different analysts.

that of the USP/Ph Eur induction port using two commercially available pMDIs of the same type (active ingredient SS).[10] Generally speaking DPIs are less readily used for the treatment of paediatric patients, with MDIs the more common choice. The test set-up used (see Figure 4) was closely similar to that described above but a test flow rate of

15 L/min (±5%) was selected. Testing at 15 L/min is more representative of the inhalation characteristics of a paediatric patient and there is archival calibration data for the NGI at this air flow rate.[11]

Whilst it could be argued that, in the clinical situation, a small child would likely have been prescribed a valved holding chamber (VHC) for use with their pMDI, a VHC would have retained much of the coarse component of the dose from the inhaler, preventing it from reaching the inlet of the C-AIT. The inclusion of a VHC was therefore considered inappropriate, since the purpose of the study was to characterise the performance of the C-AIT alone.

Details of the test programme, which involved the use of multiple analysts and devices, are shown in Figure 5. Each test measurement was the result of ten actuations of the inhaler with each actuation process involving a five second shake and a two second actuation followed by a five second hold, prior to removal of the device for the next test.

Figure 6 shows the measured mass deposition profiles for the inlet and each stage of the NGI, based on the total mass/actuation emitted during testing.

The bulk of the SS dose was recovered from the inlet in either case, regardless of which analysts carried out the measurement and which device was used. However, as with the AIT, significantly more of the dose deposits in the C-AIT than in the USP/Ph Eur induction port; 82.4 ±1.6% compared with 67.4 ±2.1%. Both of the devices tested delivered similar results.

Figure 7 shows cumulative mass-weighted APSDs for the two inlets and includes data from both devices. These results con-
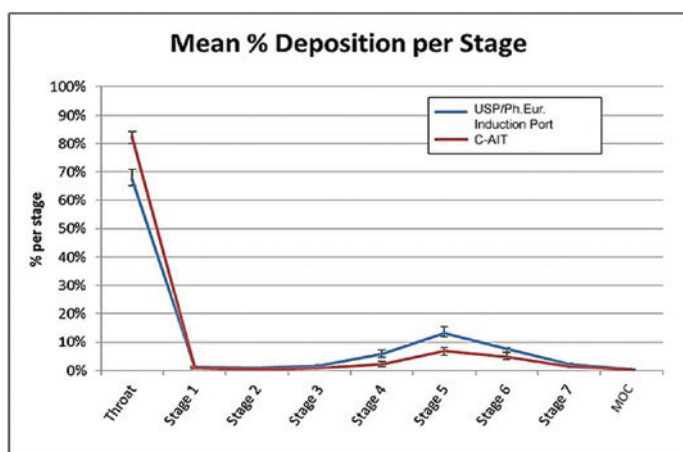

Figure 6: Deposition profiles for each stage of the NGI including the inlet for the USP/Ph Eur induction port and C-AIT measured at 15 L/min. Error bars denote max/min range of data.
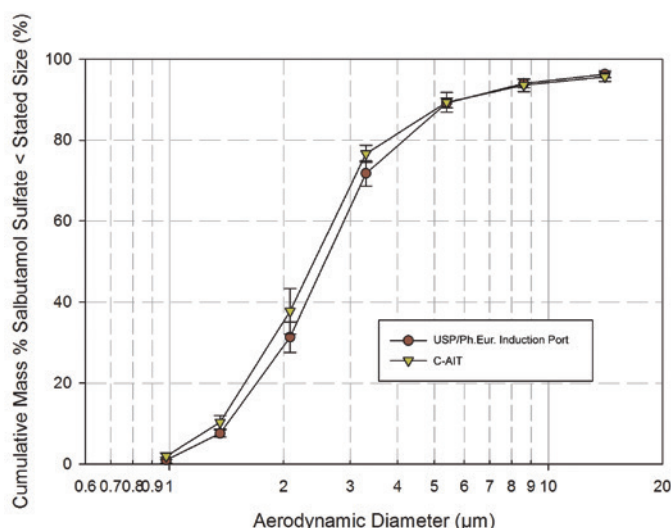

Figure 7: Cumulative mass-weighted APSDs for pMDI-delivered SS for the USP/Ph Eur induction port and C-AIT.

Measure	USP/Ph. Eur. Induction Port	C-AIT
MMAD (µm)	2.6 ± 0.1	2.4 ± 0.1
GSD	1.77 ±0.04	1.81 ± 0.16
$FPF_{<5.0µm}$ (%)	28.0 ± 1.2	15.6 ± 1.6
$FPM_{<5.0µm}$ (µg/actuation)	28.2 ± 2.1	16.0 ± 1.3

Figure 8: APSD metrics for the C-AIT and USP/Ph Eur induction port (Mean ± SD).

firm that the C-AIT, like the AIT, results in a small but discernible shift in the APSD to finer particle sizes, when compared with the USP/Ph Eur induction port. This observation is highlighted by the summary data in Figure 8 which shows a statistically significant reduction in MMAD attributable to the use of the C-AIT; a shift in MMAD from 2.6 µm to 2.4 µm. The change is reflected in a corresponding reduction in FPF (based on delivered dose) when the C-AIT is used; 15.6% compared with 28.0% with the USP/Ph Eur induction port. GSD remains largely unchanged.

In summary the C-AIT, like the AIT, captures more of the emitted dose and preferentially retains coarser particles, inducing a small but significant shift in the MMAD. Interestingly the magnitude of the shift in MMAD to finer sizes was smaller for the C-AIT than for the AIT, 7% (from 2.6 µm to 2.4 µm) relative to 16% (2.5 µm to 2.2 µm). This difference may be attributable to the different flow rates applied during testing, and could suggest that the inability of the USP/Ph Eur induction port to mimic actual mouth throat deposition behaviour becomes more pronounced as turbulence in the respiratory tract increases.

THE BIGGER PICTURE

While the focus on a more anatomically correct inlet for OIP testing is important, other features of OIP testing also call for some refinement to meet the goal of better IVIVRs. A prime example is the inhalation profile applied during APSD measurements.

In standard CI testing (for DPIs) the applied inhalation profile is simply a square wave profile: an almost instantaneous on/off switch, taking the flow rate from zero L/min to a pre-determined, constant value for a short duration and back to zero L/min again. This is achieved through the use of a timed, rapid-acting solenoid valve in conjunction with a vacuum pump. This approach, developed to be compatible with the method of operation of cascade impactors (which are designed to work under constant flow rate conditions), clearly does not reflect the capabilities of a typical patient. It is, however, like the standard USP/Ph Eur induction port, highly suitable for QC testing due to its simplicity and reproducibility.

During product development the broader requirement is to assess how the patient's inhalation profile impacts the success, or otherwise, of drug delivery and to what extent these profiles differ from those applied during routine testing. Consideration should be given to:

- the total volume inhaled
- the shape of the profile, which may not be uniform or symmetrical
- the peak flow achieved
- the rate of acceleration of the flow during the initial ramp up, which may be critical to aerosolisation of the dose (especially for passive DPIs) during the dose emission phase.

The commercial availability of cost-efficient breath simulators (exemplified by the BRS range from Copley Scientific) allows researchers to apply more representative inhalation profiles during OIP testing. To enable CI measurements simultaneously under constant flow rate conditions these breath simulators are applied in combination with a mixing inlet (see Figure 9). With a mixing inlet the flow rate applied through the OIP can be independently varied to allow application of realistic inhalation profiles (as perhaps measured in clinic) whilst the flow rate through the CI is maintained at a constant flow rate to deliver calibrated performance.[12]

With this test set-up the performance of an OIP can be assessed over a broad range of realistic inhalation profiles, in a way that is entirely consistent with the application of QbD. It becomes possible to assess the sensitivity of drug delivery to the inhalation strength of the patient for example, and/or specifically to test a product for a certain patient group with an atypical inhalation profile. Furthermore this set-up also enables the more robust demonstration of *in vitro* bioequivalence since it can be shown that the performance of a generic mirrors that of a reference inhaled drug product over a range of realistic inhalation profiles, not just a single square-wave profile.

A multi-faceted approach to the refinement of OIP testing is clearly critical as the industry works towards better IVIVRs. More anatomically correct representation of the mouth-throat is one part of the solution; more accurate simulation of the inhalation profile is another. In combination these refinements substantially enhance the value of *in vitro* testing, making it a far more relevant tool for the development of new and generic OIPs.
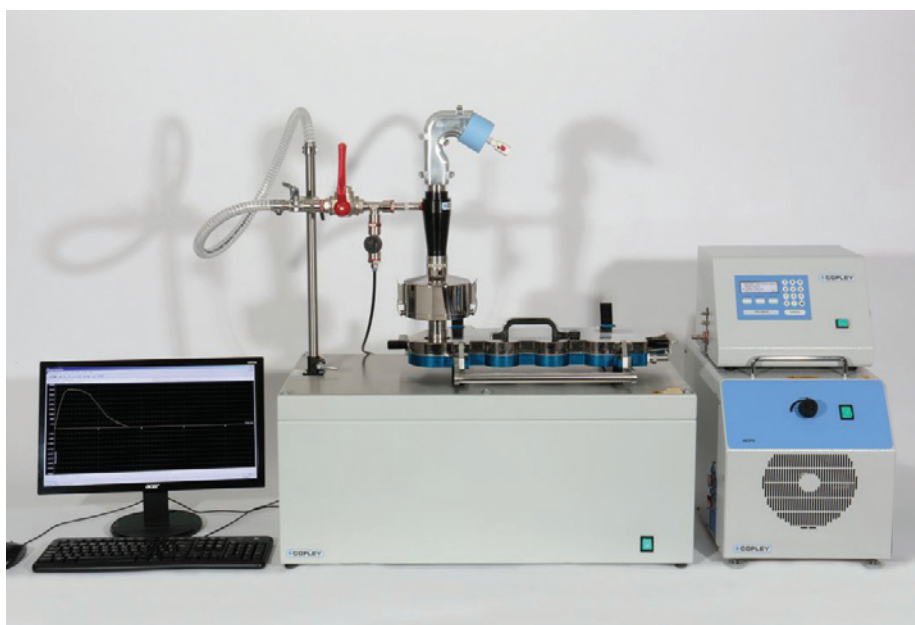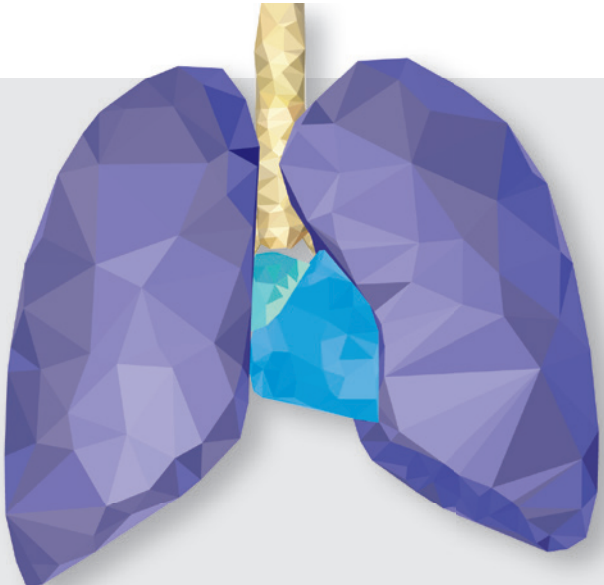

Figure 9: An optimised test set-up for procuring good IVIVRs in APSD testing of OIPs.

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Celanese

NEW MATERIAL DEVELOPMENTS FOR MEDICAL DEVICES: POLYMERS WITH IMPROVED TRIBOLOGY

Here, in the context of the interactions and friction between moving parts in contact inside drug delivery devices, particularly inhalers, Kirsten Markgraf, PhD, T&I Product Development, POM, and Wendy Johnson, Medical Marketing Manager, Engineered Materials, both of Celanese, review the performance of various polyoxymethylene acetal copolymer grades, and introduce two new grades optimised for sliding applications.

INTRODUCTION

Many drug delivery devices contain moving parts. As these parts move, such as in an inhaler, they must effectively slide against other parts. The device must function smoothly with a low co-efficient of friction and low noise or wear. This performance has to be achieved in complex design environments including movements against different types of materials, operating across a range of temperatures and chemical environments and with a range of speeds and forces in operation.

This paper reviews the performance of different polyoxymethylenes (POM) acetal copolymer grades, with and without exter-

nal lubricants. It also includes the review of two new grades of tribologically modified polymers that operate effectively without the aid of external lubricants.[1] These are specifically suited for use in sliding applications *versus* a wide range of polymeric counterparts as well as metals.

POLYMER COMBINATIONS

When identical unmodified polymers slide against each other, there is a tendency towards high friction and it is best to avoid these pairings.[2] However, it may be the case that these combinations are favourable because of other interactions and/or requirements, e.g. laser marking, suitable
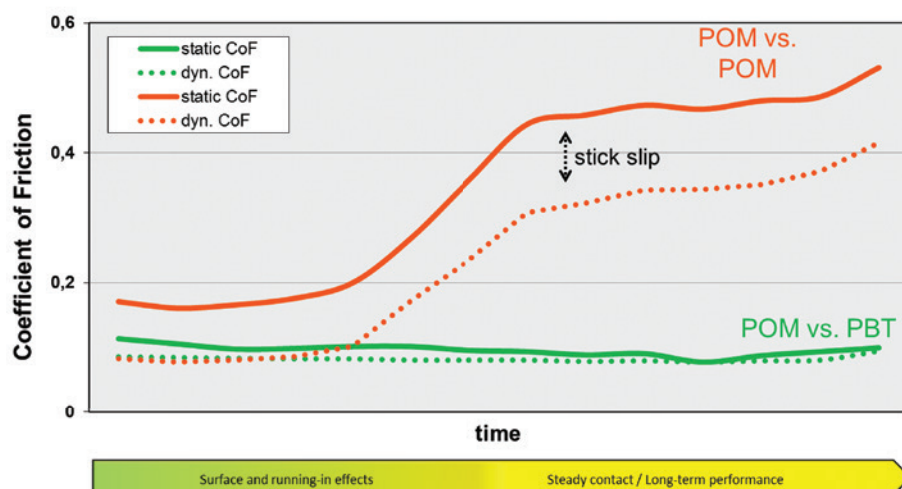

Figure 1: Sliding behaviour of POM/POM versus POM/PBT.

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sterilisation techniques or mechanical specifications. For combinations of unmodified POM-on-unmodified POM the static and dynamic co-efficient of friction shows a large difference resulting in a high risk of noise during sliding.[3]

Changing to a combination of dissimilar materials may provide a solution. For example, a POM-on-POM combination may generate noise whilst a POM-on-polybutylene terephthalate (PBT) pairing may run silently during use (Figure 1). This is due to the relatively small difference between the static and dynamic co-efficients of friction in the POM-on-PBT combination.

USE OF EXTERNAL LUBRICATION

Lubricants on the surface of the part create a film during operation and provide exceptionally low friction between sliding components (Figure 2). Lubrication can either be achieved through coating parts (post-siliconisation) or internal lubrication. The downside of external lubrication is the management of the secondary process, potential migration of the lubricant to undesired locations in the device and the drug, chemical resistance issues, device-to-device consistency, and efficiency after long-term storage of the device.

USE OF INTERNAL LUBRICATION

Internal lubrication of polymers is achieved either in production via the use of master batches in the injection moulding process, or as a ready-to-use compound directly from the raw material supplier. It is difficult to match the extremely low levels of friction achievable by surface film lubrication. However, when the right lubricant is used for the combination of base polymers involved, excellent results can be achieved. Some lubricants have excellent dispersion within the polymer (e.g. waxes) and migrate to the surface of the polymer during injection moulding. Others form discrete pockets of lubricant (e.g. PTFE) requiring a running-in phase to get some initial surface wear to optimise lubrication potential.

Figure 3 gives an overview of the sliding performance of unmodified POM-on-unmodified POM, resulting in the highest coefficients of friction as well as *versus* POM with different tribological modification (internal lubricants).

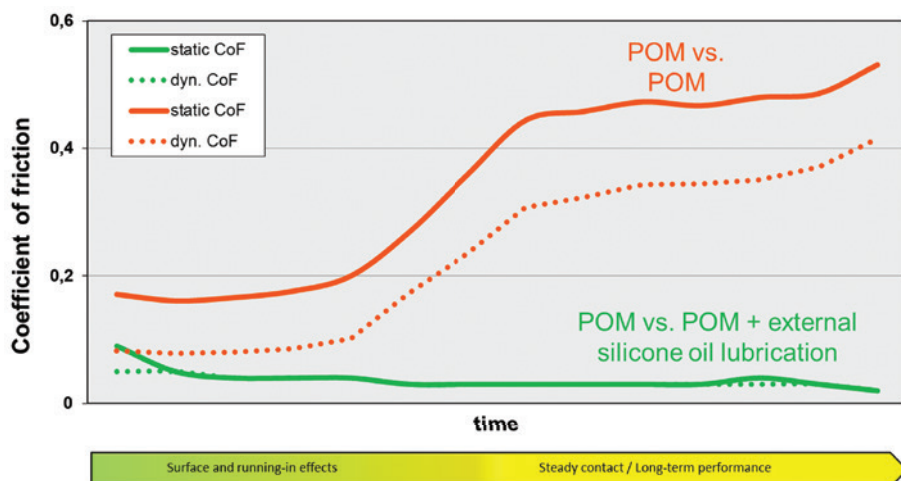Modifiers that improve sliding performance in POM may strongly influence the

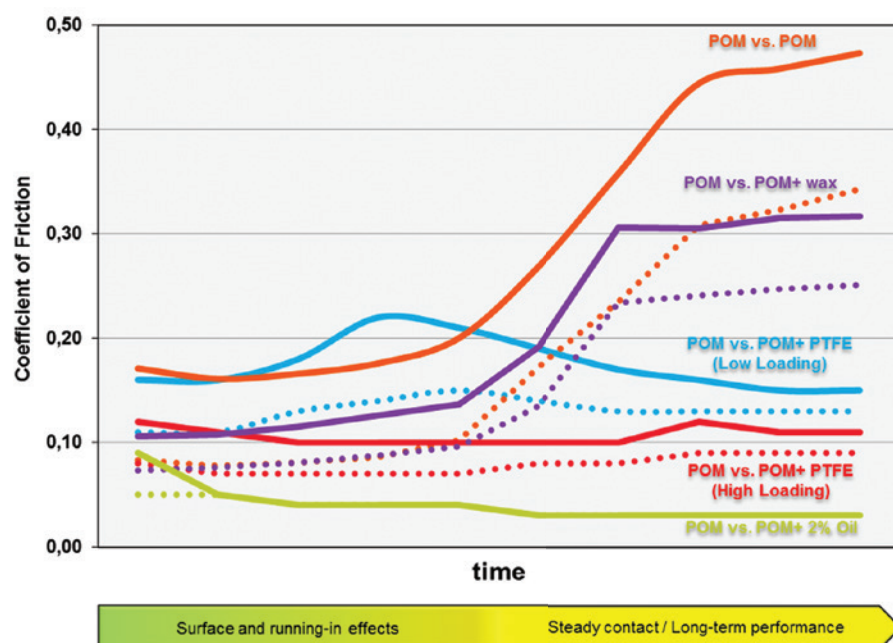Figure 2: Effect of external lubrication (silicone oil).

Figure 3: The influence of different internal lubrication on co-efficient of friction (CoF). (Dotted lines = dynamic CoF. Solid lines = static CoF.)
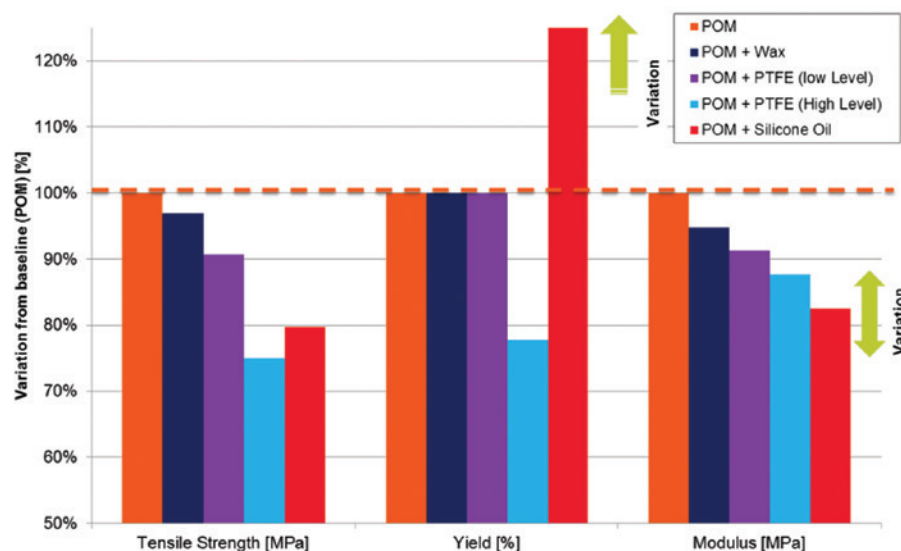
Figure 4: The influence of different internal lubricants on mechanical properties.
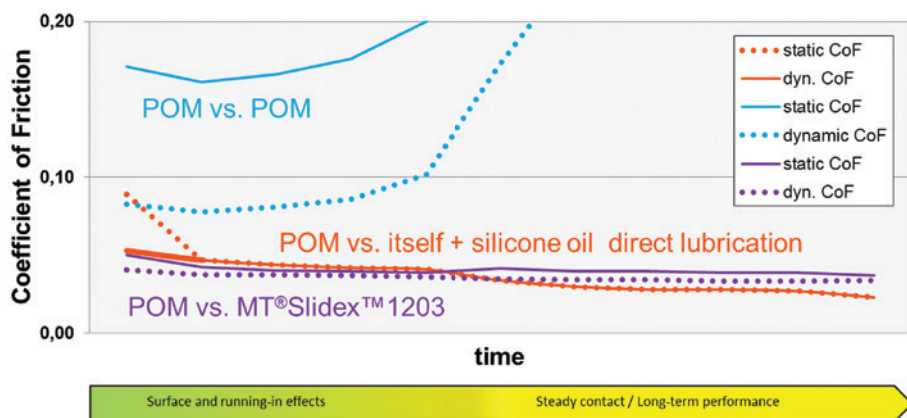
Figure 5: Sliding behaviour of Hostaform® MT® SlideX™ 1203 versus unmodified POM (MT®8U01) in comparison with external lubrication.

mechanical properties of the material, as depicted in Figure 4. Silicone oil is commonly used but can result in a significant plasticising effect on the polymer. Waxes provide modest improvement in tribological performance at low cost while PTFE provides further improvement, but with a significant running-in period to achieve full effect. At higher concentrations there is a mould deposit risk.

LATEST DEVELOPMENTS

Recently developed medical POM grades, the new Hostaform MT® SlideX™ grades from Celanese, exhibit low co-efficients of friction *versus* unmodified POM such as Hostaform MT®8U01, and with a similar stick-slip performance as external lubrication of MT®8U01 with silicone oil (Figure 5).

The new grades enable low friction in POM-on-POM pairings and with a range of other counterparts (Figure 6), without sacrificing mechanical performance.

The two new Hostaform® MT® SlideX™ grades are distinguished by their viscosities. Hostaform MT® SlideX™ 1203 is a standard-flow injection moulding grade. A high-flow version, Hostaform MT® SlideX™ 2404, is offered for thin-walled, complex part designs. The new Hostaform MT® SlideX™ grades are the latest development in the area of tribologically modified polyoxymethylene to meet low co-efficients of friction *versus* a variety of thermoplastics with medical compliance.

CONCLUSION

There is not one commercial speciality polymer that can meet all the demands of the tribological systems of drug delivery devices. However, the new Hostaform MT® SlideX™ grades are supported by data demonstrating very low friction, low wear and low noise performance when used with a broad range of partner materials, including POM-on-POM combinations and, furthermore, demonstrate excellent mechanical behaviour.

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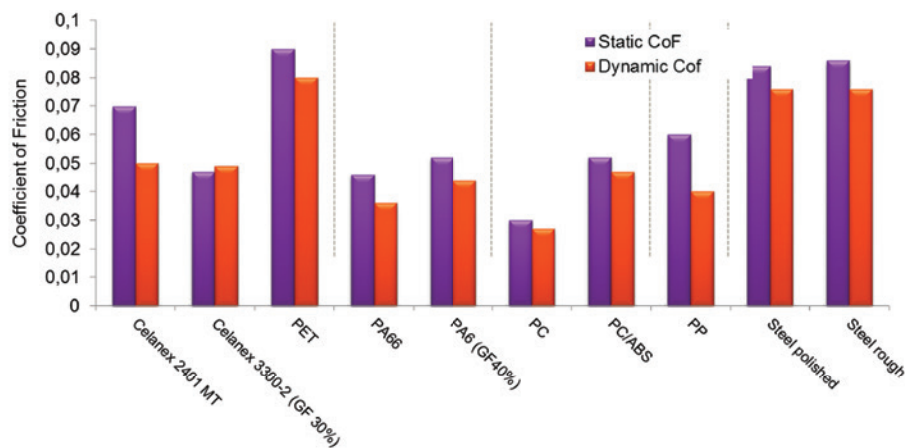3. *According to VDA 230-206 "Examination of the stick-slip behaviour of material pairs Part 1".*

Figure 6: Co-efficient of friction of Hostaform® MT® SlideX™ 1203 versus other thermoplastcs /metals.

MDI PROPELLANTS – IS THE POPULARITY OF HFA 227EA SET TO GROW?

In this piece, Tim Noakes, PhD, Medical Propellants Commercial Manager, Mexichem Fluor, predicts a rise in demand for HFA 227ea – a less common MDI propellant than the better-known HFA 134a.

Inhalation aerosols, usually called Metered Dose Inhalers (MDIs), provide an effective, easy-to-use method of delivering medication in an atomised form.

These products require the use of a propellant to deliver the dose and there are two approved propellants in use today, both belonging to the class of hydrofluoroalkanes (HFAs). These are HFA 134a (1,1,1,2-tetrafluoroethane) and HFA 227ea (1,1,1,2,3,3,3-heptafluoroethane), both of which have been in use since passing extensive toxicology studies in the 1990s. HFA 134a is currently the most widely used but in this article I wanted to focus on its specialist cousin HFA 227ea – a product which we believe will significantly grow in use in the near future.

In use, medical HFAs need to deliver a complicated balance of properties. Most MDI formulations consist of an insoluble finely ground drug, suspended in liquefied, pressurised HFA propellant, possibly with other ingredients such as small amounts of alcohol added as well. This formulation is held in a small aerosol can with a metering valve, such that when the valve is pressed a metered dose is atomised out of the nozzle and into the patient's respiratory tract.

The key goal for the formulation chemist in developing these medications is to produce something which, when emitted from the aerosol can as a dose, will contain the right amount of the drug in a highly dispersed form so that it can be inhaled, throughout the entire shelf life of the product – commonly a period of two years and sometimes longer.

To achieve this, the chemist has to meet the following requirements:

1. The drug should not chemically decompose under possible conditions of storage

2. The suspended drug particles should not change their particle size distribution, in particular there should not be any loss of fine particles and growth of coarse particles, by any recrystallisation processes

3. The suspended drug may well settle to the bottom of the can when not in use, but it is important that a single shake will re-suspend it in the propellant, so that a good dose can be taken out of the can when the unit is used.

It is in addressing these three requirements that the need for the specialist properties of 227ea arises. Figure 1 contrasts the key properties of HFA 227ea with those of HFA 134a.

The most important difference between the two HFAs for an MDI formulation is the liquid density. The difference between approximately 1.2 and 1.4 may not look like much, but many drugs that are used in MDIs have crystal densities in this range so the choice of the HFA can determine whether a particular drug crystal floats, is neutrally buoyant, or quickly sinks to the bottom. If the drug crystal sinks rapidly then it is harder to get a reliable dose, a problem which is further complicated by a tendency for crystals to stick together.

> "The most important difference between the two HFAs for an MDI formulation is the liquid density. The difference between approximately 1.2 and 1.4 may not look like much, but many drugs that are used in MDIs have crystal densities in this range so the choice of the HFA can determine whether a particular drug crystal floats, is neutrally buoyant, or quickly sinks to the bottom"

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In some cases, the polarity of HFA 134a can make the recrystallisation problem worse as indeed can the higher level of moisture affinity. This also has a very serious impact on chemical stability, as uptake of moisture is one of the most common reasons for decomposition of drugs on storage in these aerosols.

Although generally speaking problems of this nature with HFA 134a are few and far between, in some cases HFA 227ea has proven the better choice in addressing these issues. Recognition of this has seen its adoption for a small but growing number of formulations, including some highly successful products. One example is AstraZeneca's Symbicort formulation, a blend of formoterol (long-acting beta agonist) and budesonide (second-generation corticosteroid).

Mexichem expects that demand for HFA 227ea is likely to grow in part because formoterol is being used in an increasing range of MDI formulations, and HFA 227ea has proved invaluable in maintaining its stability for an effective shelf life.

One factor limiting the adoption of HFA 227ea in the past has been the perceived weakness in the 227ea supply chain.

Property	HFA 134a	HFA 227ea
Boiling point (oC)	-26.2	-16.5
Liquid pressure at 25 oC (bar)	5.65	3.54
Liquid density at 25 oC (g/cc)	1.21	1.39
Polarity (solvent power)	Polar, like a weak alcohol	Less polar, more ether-like.
Moisture affinity (ppm water saturation, 20 oC)	~1000	~500

Figure 1: Comparison of key properties of HFA 134a and HFA 227ea.

Production as a medical grade – purification under rigorous quality control in compliance with key pharmaceutical industry codes such as current Good Manufacturing Practice

HFA 227ea through the acquisition of DuPont's medical HFA 227ea business.

Mexichem is the largest supplier in the medical propellants business and a major

"Mexichem's recent investment in HFA 227ea ensures that it can offer a reliable source of HFA 227ea as demand increases"

(cGMP) – is reliant on wider industrial production. In the case of HFA 134a there is a large global supply for industrial HFA 134a for refrigeration and foam blowing applications but the volume and range of applications is lower for HFA 227ea. Mexichem has now strengthened its supply chain for

manufacturer in the wider fluorochemicals industry, from the extraction of the mineral fluorspar through to production into many fluorochemical products. As such Mexichem's recent investment in HFA 227ea ensures that it can offer a reliable source of HFA 227ea as demand increases.

COMPANY PROFILE: NEMERA

Nemera

In 2014, the healthcare business formerly known as Rexam Healthcare Devices became Nemera. This name change followed the May 2, 2014 acquisition by Montagu Private Equity. Nemera continues to operate with the same management team and its choice of name signifies a renewed commitment to its mission of providing patients with safe and accurate delivery devices.

NEMERA'S INNOVATION CENTRE

Innovating for patients is at the core of Nemera's mission. More than 50 engineers and experts work to achieve this at the Innovation Centre at La Verpillière, near Lyon, France.

The scope of the Innovation Centre includes the collection of patients' insights, market watch, concept generation, IP monitoring, regulatory expertise, detailed risk-based design, design for manufacturing and support to plants for product life-

Figure 1: Inhalia® new-generation valves for pMDIs.

other), creative design and usability assessment including Human Factors (HF) studies, are central to product development. The Innovation Centre carries real-world evaluations, through impartial volunteers and collects user feedback. Sophisticated technologies, like fast-camera tracking, give engineers an inside view of the way the device is used, making it safe and accurate for the patient.

Proprietary Devices & Contract Development
We apply the same quality-oriented process to the development of proprietary devices and to customised solutions under contract

cycle management and problem solving when appropriate.

Patient Insights & Human Factors Studies
Technical expertise and patient usability always work hand-in-hand. Along with the many fields of technological expertise (like material, mechanical and manufacturing engineering, mathematical models and

> Advancia® is a new range of nasal spray pumps

with laboratories. The development quality team guarantees full compliance not only of the final device but of all the development chain. Strong programme management ensures that the project is delivered on time and within budget.

A WORLD LEADER IN DRUG DELIVERY SOLUTIONS

Nemera is one of the world leaders in the design, development and manufacturing of drug delivery solutions. Nemera's expertise encompasses five modes of delivery: ophthalmic (preservative-free droppers), nasal, buccal, auricular (sprays pumps, etc); pulmonary (DPIs and standard valves for pMDIs); dermal and transdermal (dispensers); and parenteral (injectors, pens, safety devices).

More than ten million asthmatics rely everyday on devices manufactured by Nemera.

Pulmonary
Consistency and reliability are critical for respiratory patients. Inhalia® (see Figure 1) is a new generation of valve for pressurised metered dose inhalers (pMDI).

Nasal, Buccal, Auricular
Following the SP270, a standard spray pump for ear, nose and throat, Advancia® is a new breed of pharmaceutical pump combining user-independence and preservative-free features in one single system. Advancia® offers a new alternative to improve treatment compliance in an increasingly demanding nasal spray market.

Parenteral
Nemera's Safe'n'Sound® device provides safety from needle-stick injuries. Adding a passive automated safety feature to prefilled syringes, Safe'n'Sound® protects patients and caregivers from contamination by blood-

NEMERA IN FIGURES
- 4 plants in Europe and the US
- 50 engineers and experts working at the Nemera innovation center
- >1,300 employees
- >30,000 square meters of manufacturing clean-rooms

Contact:

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"More than ten million asthmatics rely everyday on devices manufactured by Nemera"

Figure 2: Advancia® user independent nasal spray pumps.

borne diseases. Robust and versatile, it comes in different formats and can be combined with ergonomic accessories.

Ophthalmic

Preservatives are harmful to patients' eyes and may jeopardise adherence to treatments, therefore Novelia® is the user friendly, preservative-free eye dropper with a precision blue tip. Novelia® is now commercialised in four continents and it is the only preservative-free eye dropper on the US market.

Dermal/Transdermal

Sof'Bag™ is a high-performance airless dispensing device designed especially for pharmaceutical gels and creams. It brings precise dosing and protection for topical and transdermal formulations.

A NAME THAT STANDS FOR LIFE & EFFICIENCY

The name Nemera comes from two sources: "Emera" from Greek meaning "day" and suggesting renewal, fresh hope and life; and "Nemer" from Hebrew and Arabic, meaning "leopard" and suggesting swiftness, efficiency and agility.

Nemera CEO Marc Haemel commented: "We work hand-in-hand with pharmaceutical companies to design, develop and manufacture the drug delivery devices that help patients every day.

"There is no limit to Nemera's ambition to serve patients. We already market devices in over 40 countries for millions of users. We'll keep investing in new products and in state of the art manufacturing equipment, to help even more patients with high quality devices all over the world."

Nemera provides solutions for the pharmaceutical industry, including standard innovative products, development of custom devices and contract manufacturing. Montagu has also bought Rexam Prescription Products, the industry leader in prescription packaging for over 100 years, which is now known as Centor.

COME AND MEET NEMERA AT RDD EUROPE: TABLE #30

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Inhalia®

A HIGH PERFORMING pMDI **METERING VALVE** PLATFORM THAT PATIENTS CAN COUNT ON

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Catalent
INHALATION

NEW

Catalent Acquires Micron Technologies

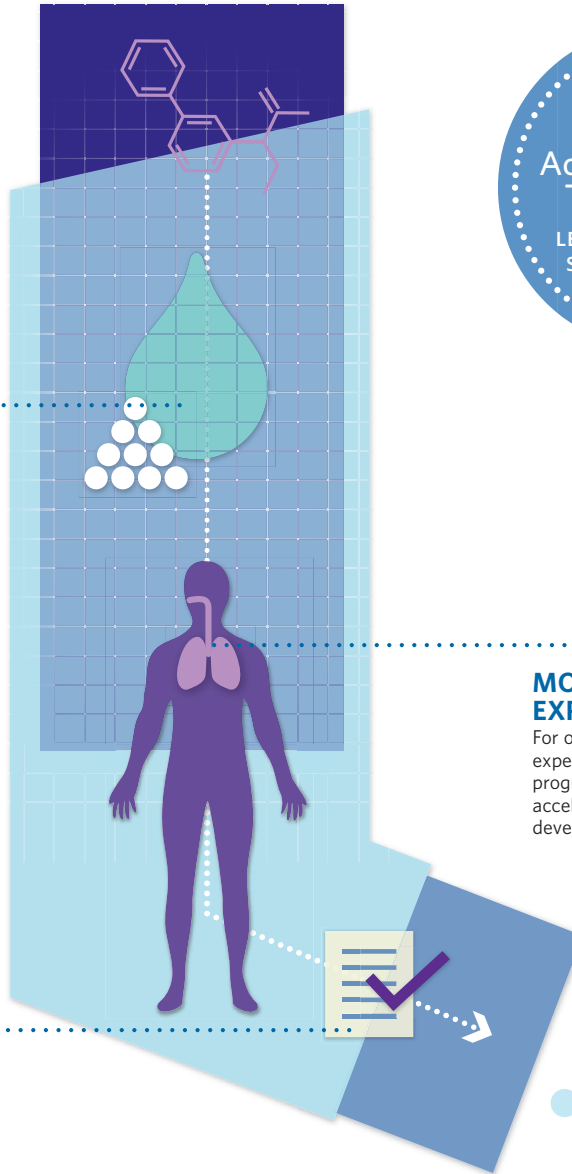**LEADER IN PARTICLE SIZE ENGINEERING**

BROADEST DEVELOPMENT CAPABILITIES

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