



SCALING UP FOR HIGH DOSE DELIVERY TO THE LUNGS

PULMONARY & NASAL DELIVERY







ONdrugDelivery Issue Nº 72, December 1st, 2016

PULMONARY & NASAL DELIVERY

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

2017 EDITORIAL CALENDAR

- Jan Ophthalmic Delivery
- Feb Prefilled Syringes
- Mar Skin Drug Delivery:
- Dermal, Transdermal & Microneedles
- Apr Pulmonary & Nasal Drug Delivery
- May Injectable Drug Delivery: Devices Focus
- Jun Connected Delivery Devices
- Jul Novel Oral Delivery Systems
- Sep Wearable Injectors
- Oct Prefilled Syringes
- Nov Pulmonary & Nasal Delivery

SUBSCRIPTIONS:

9-10 issues of ONdrugDelivery Magazine published per year, in PRINT & PDF.

PDF subscription is always completely **free**.

PRINT subscription costs **£189/year**. Print subscription includes delivery of a printed copy of each issue to one address anywhere in the world.

E: subscriptions@ondrugdelivery.com

EDITORIAL AND ADVERTISING:

Contact: Guy Fumess, Proprietor & Publisher T: +44 (0) 1273 47 28 28 E: guy.fumess@ondrugdelivery.com

MAILING ADDRESS:

Frederick Furness Publishing Ltd The Candlemakers, West Street, Lewes, East Sussex, BN7 2NZ, United Kingdom

ONdrugDelivery Magazine is published by Frederick Fumess Publishing Ltd. Registered Office: The Candlemakers, West Street, Lewes, East Sussex, BN7 2NZ, United Kingdom.

Registered in England: No 8348388. VAT Registration No: GB 153 0432 49. ISSN 2049-145X print ISSN 2049-1468 pdf

Copyright © 2016 Frederick Furness Publishing Ltd All rights reserved



The views and opinions expressed in this issue are those of the authors. Due care has been used in producing this publication, but the publisher makes no claim that it is free of error. Nor does the publisher accept liability for the consequences of any decision or action taken (or not taken) as a result of any information contained in this publication.

Front cover image "CFD plot from TwinMax inhaler, showing flow stream lines coloured by velocity", courtesy Hovione Technology. Reproduced with kind permission.

4 - 6	Expert Overview: Learning to Walk Before We Run: Basic Problems With Inhalers Persist, & Why it is Worth Solving Them David Harris, Respiratory Drug Delivery Specialist PA Consulting Group
8 - 11	The Capsule-based DPI, an Environmentally Friendly and Efficient Drug Delivery Dosage Form Susana Ecenarro Probst, Director of Scientific Business Development Qualicaps
12 - 15	Patient Preference of Respiratory Device Training & Educational Tools Paul Sullivan, Associate Director, Business Development and Craig Baker, Executive Vice-President Noble
18 - 21	Leverage Technology to Overcome Pulmonary Drug Delivery Challenges Jean Vuillecard, Innovation & Product Manager and Eric Dessertenne, Head of Commercial Operations & Business Development BioCorp
24 - 27	Advancia®: a True Platform & Innovative System Offering Efficient Nasal Dose Delivery Pascale Farjas, Global Category Manager ENT Products Nemera
30 - 33	Scaling Up for High Dose Delivery to the Lungs João Ventura Fernandes, Business Development Manager, Gonçalo Rebelo de Andrade, Director and Peter Villax, Chief Executive Officer Hovione Technology
34 - 36	Selection of Equipment for Dry Powder Inhalers Harry J W Peters, Product Application Specialist Inhalation and Gerald A Hebbink, Scientist DFE Pharma
38 - 42	Optimising Analytical Strategies for the Demonstration of Bioequivalence in a Generic Nebuliser Déborah Le Pennec, Research Technican University of Tours Laurent Vecellio, Scientific Director Aerodrug, DTF Medical Paul Kippax, Team Leader, Advanced Materials and Stephane Rouquette, European Business Manager, Biosciences Malvern Instruments

Device training happens here.

There's life beyond chronic conditions. Distractions, anxiety and understanding correct administration technique can all affect compliance. Studies suggest 61% of patients don't completely read the IFU¹ and 12% of patients have proficient health literacy.²

Will your patients correctly administer their drug delivery device?

nobe Onboarding and Device Training

le. (2015, November). The link between device training and patient compliance. Poster session presented at PDA-Universe of Prefiled Syringes 201 tria. 2, Kessels, R. P. (2003, May). Patients' Memory for Medical Information. Retrieved from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3947

LEARNING TO WALK BEFORE WE RUN: BASIC PROBLEMS WITH INHALERS PERSIST, & WHY IT IS WORTH SOLVING THEM

By David Harris

The humble pressurised metered dose inhaler (pMDI) is celebrating its 60th birthday this year and it has certainly stood the test of time. Not a lot has changed since it was introduced all those years ago. In the region of 680 million pMDIs are used annually¹ to treat people suffering with asthma or COPD (chronic obstructive pulmonary disease), which equates to approximately 2,500 shots fired around the world every second. These numbers are astonishing and, unfortunately, numbers that are on the increase as incidence of respiratory diseases continue to rise.

The pMDI is tremendously popular – the first choice of medication in many countries – yet 90% of asthmatics and COPD patients cannot use them correctly.² This shouldn't really come as a surprise though – let's face it, there are a number of well-known challenges pMDIs present to patients...

The first challenge is that patients are instructed to "breathe in deeply and slowly".

There is a substantial body of research that shows just how beneficial inhaling at a low flowrate is, in terms of increasing deeplung deposition, reducing mouth and throat deposition, and achieving consistency in the delivered dose. Yet pMDIs are very easy to inhale through - they offer practically zero resistance to the airflow, meaning that patients are often able to inhale at ten times the optimal flowrate. And why wouldn't they? After all, it's in their best interest to get the event over with as quickly as possible, right? Wrong, actually. And what flowrate constitutes "slowly" anyway? It's very subjective. Yet the benefits of inhaling below 40 L/min are clear and demonstrated³ - lung deposition can be as high as 50% compared with just 8-12% for those who choose to inhale as quickly as possible.

Compounding this already significant issue, is the fact that standard pMDIs require the user to co-ordinate the "680 million pMDIs are used annually¹ to treat people suffering with asthma or COPD, which equates to approximately 2,500 shots fired around the world every second ... The pMDI is tremendously popular yet 90% of asthmatics and COPD patients cannot use them correctly.² This shouldn't really come as a surprise though - let's face it, there are a number of well-known challenges pMDIs present to patients."

pressing of the canister correctly with their inspiratory manoeuvre. This is a difficult task to achieve, and continues to thwart many experienced asthmatics, even those with the best intentions. Over the six decades that the pMDI has been in existence, only two automatically (breath)-actuated products have ever made it to market – 3M's Autohaler and IVAX's (now Teva's) Easi-Breathe.

There are several breath-actuated pMDIs currently undergoing development but engineering a suitably robust and scalable mechanism is particularly challenging, due to the huge difference between the force required to press the canister (typically 25-30 N) and the tiny force that can be created by someone inhaling (typically a small fraction of one Newton). This difference – which is several orders of magnitude –



David Harris Respiratory Drug Delivery Specialist T: +44 1763 267 608 E: david.harris@paconsulting.com

PA Consulting Group

Cambridge Technology Centre Melbourn Herts SG8 6DP United Kingdom

www.paconsulting.com

means that designing a mechanism that fires correctly when a patient inhales but doesn't fire when you accidentally drop the primed inhaler, for example, is exceedingly difficult. Unfortunately, clever, automatic inhalers such as these end up costing much more to produce, and consequently are only prescribed to patients who are deemed to have significant issues with standard pMDIs.

So given that asthma and COPD are both on the increase, together with the direct and indirect costs of non-adherence, then surely there must be a vast amount of research and development activity seeking to address these two major issues with the pMDI? I'm afraid not. There is, however, substantial time and effort being devoted to developing "smart" inhaler technology that, for example, enables inhalers to connect to smartphones and provide information such as when and where the patient took their medication.

The potential here is staggering. The metadata will have extremely high longterm value as analysis could reveal currently unknown correlations (for example, the effect of particulate concentrations on frequency of reliever use) and eventually may even pre-empt the likelihood of exacerbations. However, this recent upsurge in adding intelligent electronics to sixty year old technology raises a number of questions.

- Who owns the data?
- How is it stored and managed securely?
- Who's going to mine it for useful information?
- Who will pay the additional cost for the intelligent part of the device?
- How will the provider be recompensed?
- What patient benefit will it actually deliver?

So, whilst the potential of adding connectivity is considerable and should not be ignored, the unknowns are too, begging the question: is this really the priority? Why not fix the basic and well characterised pMDI use issues first, then add connectivity and varying levels of intelligence if it adds further value or benefit and is commercially viable?

The honest answer is that it is actually probably easier to add connectivity to pMDIs than to find solutions to their fundamental issues. Inhalers, and the science that underpins how they work, are highly complex and not very well understood. Take dry powder inhalers (DPIs) for "Higher performance, in terms of higher fine particle fraction, mathematically leaves less scope for variability and consequently will deliver better dose content uniformity. So it's a winwin; pharma companies achieve more consistency in their clinical data, and patients receive more drug where it's needed and less in the mouth and throat."

example. You have multi-phase fluid dynamics, bulk powders – often comprising a blend of three polydisperse size fractions, electrostatics, cohesive and adhesive forces – compounded by moisture-dependent capillary interaction, not to mention the vast number of influencing variables at play. It's difficult! I've heard people refer to it as "rocket science" but actually, in many ways, it's probably harder, for we can design and build very efficient rockets and, relative to inhalers, the science behind rockets is reasonably well understood.

"Looking at the cost of non adherence and suboptimal use more closely, suggests that pursuing the generic route is merely a short term solution. The resultant costs of non adherence are significantly higher than the cost of treating the condition properly in the first place. Physician visits and hospitalisations alone cost more than the global market value of inhaled products."

But inhalers need to be improved for a great number of reasons. For example, considerable resources in the inhalation devices industry are currently being focused on copying successful, off patent products in order to produce cheaper alternatives. Whilst this is an honourable and ethical thing to do, as a collective body of individuals working in this sector, it should be forefront in our minds that there are still fundamental issues with the original delivery technology that need to be solved rather than copied. Not least because pharma companies working on new chemical entities (NCEs) frequently struggle to find suitable inhaler devices to enter clinical studies with confidence, and thus often resort to conducting early studies with a nebuliser, knowing that this will not be their eventual preferred route to market.

A cursory look through any of the recent parenteral drug delivery-focused issues of ONdrugDelivery Magazine reveals how the widespread availability of true device platforms for parenteral delivery is transforming the sector, rapidly advancing and accelerating the development of products suitable for self-injection. In contrast, platform technologies in the DPI space simply don't exist, at least beyond generic, off-patent capsule inhalers. Each drug formulation and device combination is carefully tailored to meet the required regulatory standards, and this process takes a long time to achieve a robust quality product.

It typically takes between eight and ten years to develop a generic DPI product.4 If better-performing DPIs existed, as true platform offerings, developed using more modern science, engineering and analytical techniques, pharma companies would potentially have lower-risk route to market available to them. Higher performance, in terms of higher fine particle fraction, mathematically leaves less scope for variability and consequently will deliver better dose content uniformity. So it's a win-win; pharma companies achieve more consistency in their clinical data, and patients receive more drug where it's needed and less in the mouth and throat.

So why are there not more people working on developing innovative inhaler technologies? There are a number of reasons...

Firstly, it's a very cost-sensitive market and DPI device and development costs are higher than pMDIs. Secondly, globally, there is increasing pressure to reduce the cost of healthcare – and conditions that are on the rise, such as asthma and COPD, combined with increasing populations – only exacerbate this situation. It's much easier not to "rock the boat" – copying successful generic products to offer lower cost products is in many ways a sensible thing to do despite the problems in the usability of pMDIs.

However, looking at the cost of non adherence and suboptimal use more closely suggests that pursuing the generic route is merely a short term solution. The resultant costs of non adherence are significantly higher than the cost of treating the condition properly in the first place. Physician visits and hospitalisations alone cost more than the global market value of inhaled products.5 Furthermore, these are only the first-order costs and factoring in second-order costs such as time off work it soon becomes very clear that addressing the fundamental issues can lead to substantial cost savings on a global scale. The questions then become: who benefits from these savings, and how will the companies who have found technical solutions be recompensed for their effort and insight?

There are additional advantages, beyond saving money, that result from driving inhaler technology forward. Many systemic drugs require higher payloads and tighter control of the delivered fine particle dose than current inhaler technology permits. Some of the notable products that have made it to market, such as Mannkind's inhalable insulin, Afrezza, have relied on novel particle engineering in order to achieve regulatory approval - device technology alone wasn't sufficient. Perhaps if suitable aerosolisation platforms existed, the time to market for such products could be reduced, and research for the pulmonary delivery of drugs for therapies beyond asthma and COPD would be a more attractive proposition.

The rate of advancement of computers, tablets and smartphones, combined with

progressive manufacturing technologies and new and novel materials, is in some ways overwhelming for pharma companies. Inhaler device technology is seriously lagging, with only connected and smart devices showing any real innovation or promise within the sector. Whilst there is a lot of ongoing research aiming to improve formulations, devices, and increase understanding, it takes many years for laboratory-scale research to translate into commercial products that benefit the patient.

What's required is firstly recognition and then acceptance that fundamental issues with inhaler products persist. We need a concerted effort to improve these basic shortcomings, and a focus on building future platform technologies that will benefit the patient and provide pharma companies with a more efficient route to take NCEs to market. Valuable lab-based research projects need to be identified, prioritised, and adequately funded in order to reduce the long timescales and relatively low likelihood of success. Only then will the escalating costs resulting from non adherence and sub optimal inhaler use be truly within our control.

REFERENCES

- 1. Howlett D, "Generic Products on Emerging Markets". Presentation at 5th Medicon Valley Inhalation Symposium, Oct 13, 2016.
- "Ninety per cent of Australians with asthma use their inhalers incorrectly". Press Release, National Asthma Council Australia, July 18, 2016. (Available at: www.nationalasthma. org.au/news/2016/ninety-per-centof-australians-with-asthma-use-theirinhalers-incorrectly)
- 3. de Kruijf W, "Usability Aspects of Multi-Dose Liquid Inhalers".

Presentation at 5th Medicon Valley Inhalation Symposium, Oct 12, 2016.

- Munro S, "Keeping it in the Family Devices and Formulations for Generic Dry Powder Inhaler Products". Presentation at 5th Medicon Valley Inhalation Symposium, Oct 12, 2016.
- 5. Lareau SC, Yawn BP, "Improving Adherence with Inhaler Therapy in COPD". Int J COPD, 2010, Vol 5, pp 401-406.

ABOUT THE AUTHOR

David Harris leads the Respiratory Drug Delivery sector at PA Consulting and enjoys the challenge of balancing commercial and technical activities, saying: "One of the best things about working at PA is being surrounded by like-minded and intelligent people many of whom are leaders in their field. Drug delivery is a hugely exciting sector to work in and it offers a wide range of technical and scientific challenges. It's also very rewarding - the products that we and others like us develop have the potential to massively improve people's lives. It's a great pleasure working with clients who share these aspirations."

Mr Harris is a physicist and has been working in the field of medical device development since 1994, where he started his career in the Respiratory Physics group at Fisons. He specialises in respiratory drug delivery and enjoys applying solid aerosol science and fluid dynamics to improve the efficacy of inhaler technology. David has numerous patents and publications in this area and regularly presents at conferences.

Drug Delivery to the Lungs Conference (DDL2017)

Wed 6th – Fri 8th December 2017 💡 Edinburgh, Scotland

Save the Date!

WHAT WE DO WHAT WE ARE

CAPSULES ARE THE VERY ESSENCE OF QUALICAPS®

As such, we are uniquely positioned to provide a capsule designed and manufactured for optimal performance in Dry Powder Inhalers

Quali-V[®]-I capsules for inhaled drug delivery



Control

M. C. Marker

Better



Inner Surface Control









THE CAPSULE-BASED DPI, AN ENVIRONMENTALLY FRIENDLY AND EFFICIENT DRUG DELIVERY DOSAGE FORM

Set against the backdrop of environmental concerns over HFC propellants used in pressurised metered-dose inhalers, Susana Ecenarro Probst, MBA, Director of Scientific Business Development, Qualicaps, presents evidence supporting the adoption of dry-powder inhalers as an attractive alternative.

It has been a long and tough negotiation path since the international Montreal Protocol treaty was adopted on September 16, 1987. It was signed initially by 46 countries with the aim of regulating the production and use of chemicals, such as chlorofluorocarbons (CFCs) and halon, which were contributing to the depletion of the Earth's ozone layer. On March 2, 1989, 12 European Community nations agreed to ban the production of all CFCs by the end of the century. The phasing-out commitment of these substances for the developing countries was extended to 2010.

CFCs had multiple applications in the field of refrigeration and air conditioning systems, heat pumps, insulation foams and pharmaceutical aerosols, among others. In the medical field, respiratory devices such as pressurised metered dose inhalers (pMDIs) had been manufactured with CFC propellants since their introduction in the sixties. A new type of propellant for aerosols has since been developed, based on different technical and financial aspects, and accepted as a safer alternative to CFCs, the hydrofluorocarbon (HFC) group of chemical substances. The transition to this new propellant started in 1994 with the first non-CFC pMDI, Proventil HFA (salbutamol) which contained a hydrofluoroalkane (HFA), and continued through to the end of 2008 with some US FDA market withdrawals.

There has been much controversy in recent years around the fact that even though HFCs belong to the group of strong greenhouse gases, they were carefully selected as the best option to replace CFCs due to their lack of contribution to ozone layer depletion. Contrary to what might be assumed, HFCs have a warming effect of up to 3,800 times that of carbon dioxide,¹ and these chemical substances are currently the world's fastest growing

"HFCs have a warming effect of up to 3,800 times that of carbon dioxide,¹ and these chemical substances are currently the world's fastest growing greenhouse gases with an increase in emissions up to 10% each year.² According to the UK NHS, the greenhouse effect of current UK emissions of HFCs from inhalers was in 2013 equivalent to 8% of the UK's entire carbon footprint.³"



Mrs Susana Ecenarro Probst Director of Scientific Business Development T: +34 91 663 08 84 E: secenarro@qualicaps.es

Qualicaps

Avda. Monte Valdelatas, 4 28108 Alcobendas Madrid Spain

www.qualicaps.com



greenhouse gases with an increase in emissions up to 10% each year.² It is interesting to note that according to the UK NHS, in 2013 the greenhouse effect of current UK emissions of HFCs from inhalers was equivalent to 8% of the UK's entire carbon footprint.³

A new investigational study co-authored by the researchers at the US National Oceanic and Atmospheric Administration (NOAA) Earth System Research Laboratory⁴ shows that the contribution of HFCs to greenhouse warming could contribute to 10% of that of CO_2 by 2050 if no specific measures are taken to restrict their use.

Recently, on October 15, 2016, the 28th Meeting of the Parties (MOP28), the most important climate conference since the Paris summit in 2015, gathered 197 Montreal Protocol members in Rigali, Rwanda (UNEP News). An agreement was adopted which implies challenging the compromise to initiate a HFCs phase-down by 2019 in developed countries, reaching an 85% reduction (based on 2011-2013 levels) by 2036. Due to financial restrictions and a High Ambient Temperature (HAT), some developing countries will be expected to adhere to a freeze on HFCs consumption levels starting in 2024 and other countries such as India in 2028.

However, the existing agreements could represent a limited impact since projections indicate a significant growth in the demand for HFCs in Asia, the Middle East, Latin America and Africa due to a fast-expanding middle class in some of these countries over the next decades.

"Contrary to what it is often believed, adults with severe respiratory diseases (severe asthma or COPD or acute exacerbations) can achieve "clinically relevant" PIFR through DPIs.¹¹"

According to current global environmental concerns, respiratory inhalers are already considered to represent a sizeable contribution to planet warming because of the propellant gases used in metered dose inhalers. They are, for example, some of the most commonly prescribed medications in the UK.⁵ Thus it is essential to ensure that inhaled drugs are recommended appropriately and used correctly to avoid unnecessary waste.

Dry powder inhalers (DPIs) have proven to be a very good alternative to pMDIs. They do not require propellants and have a carbon footprint 18 times lower than pMDIs, demonstrating that DPIs are a cleaner technology. Additionally, they are considered to be equally effective for the treatment of the most common respiratory diseases, asthma and COPD.⁶⁻⁷

Drug deposition in the lungs from capsule-based DPIs has been under scrutiny in several studies over the past few years (see "Respiratory Drug Delivery, Essential Theory and Practice", Page 284, corresponding journal references included). The deposition value obtained from the Cyclohaler® (Teva, Petah Tikva, Israel). measured by gamma scintigraphy averaged 19% of the capsule dose and was similar in patients with mild or severe pulmonary impairment. However, some new particle engineering technology such as PulmoSphere® (Novartis, Basel Switzerland) particles achieved an in vivo average result of 34.3% by means of the Turbospin® device (PH&T, Milan, Italy). A different formulation using large porous particles with the AIR® inhaler (originally developed by Alkermes (Dublin, Ireland) produced a higher lung deposition average result of 51%.

In contrast, lung deposition from pMDIs produced values of around 20% and below, with a few results close to or above 40%. The higher figures came from a HFA solution formulation (QVAR®, Teva), which delivers an aerosol with a smaller mass median aerodynamic diameter than conventional pMDI suspension formulations.⁸

When analysing the factors that might influence the effectiveness of a capsulebased DPI, the following characteristics should be taken into consideration:

1. Capsule-based DPIs are breath-actuated devices

This is considered an advantage since there is no "press and breathe" action that requires co-ordination, as with many pMDIs (except for breath-actuated pMDIs). The main consequence of poor inhaler handling, such as actuating the pMDI too late, is a low or variable lung dose that in turn leads to variable lung deposition. However, with capsule-based DPIs, some patients may not possess "Several investigations have shown that the capsule plays an important part in delivery from capsulebased DPIs, because not only does it participate as packaging of the formulation, but it also has a role in the aerosolisation of the powder and the dispersion of the micronised drug from the carrier after the patient has pierced the capsule and inhaled through the DPI."

the required manual dexterity to load capsules, especially elderly patients or children, who could be hindered if the patient has a severe airflow obstruction.

The importance of patients receiving adequate instruction on how to use an inhaler has been addressed and emphasised at several conferences in the last years, revealing the important role that health professionals play in supporting patients by offering to monitor peak inspiratory flow rate (PIFR) and by showing them training aids.⁹

2. The aerosol formation in DPIs usually depends on the inhalation effort of the patient

There is clear evidence that the total lung deposition will increase with a higher inspiratory flow rate (IFR) due to better dispersion of the powder. However, the time at which PIFR is achieved during inhalation is also relevant and depends on the type of DPI used. It is important that the PIFR be reached as soon as possible, since the delivered dose and the powder de-agglomeration occur primarily in the early part of inhalation.¹⁰ Contrary to what it is often believed, adults with severe respiratory diseases (severe asthma or COPD or acute exacerbations) can achieve "clinically relevant" PIFR through DPIs.¹¹

The circumstance of suboptimal inhalation could cause insufficient powder disaggregation followed by a low emitted dose due to some dry powder being retained



Figure 1: Experimental methods to evaluate the aerodynamic performance of a conventional formoterol-based dry-powder formulation using two types of capsules (hypromellose and gelatin) from two manufacturers (Qualicaps[®] and Capsugel[®]).

"HPMC has risen in popularity following a significant amount of pharmaceutical research showing that gelatin capsules are not suitable for encapsulating hygroscopic products, and are chemically unstable under certain conditions. HPMC capsules have emerged in the market as the most viable alternative because of their vegetal origin, chemical stability, absence of crosslinking and low moisture content (between 4.5% and 6.5%)."

in the capsule and/or device. Additionally, the humidity (e.g. the moisture content of the capsule containing the drug powder, drastic environmental condition or exhalation during inhalation technique) is another factor that together with the inspiratory flow rate might affect the aerodynamic performance of a dry powder formulation.

Both parameters have been studied in an investigation carried out at the Laboratory of Pharmaceutics and Biopharmaceutics, Université Libre de Bruxelles (ULB, Belgium), by testing different inspiratory flow rates and by comparing the behaviour of gelatin and hypromellose (HPMC) capsules in drastic temperature and relative humidity conditions.¹² The aim of this study was an aerodynamic performance assessment of a conventional formoterolbased dry powder formulation (Formoterol content was 12 µg per 24 mg) using these conditions (Figure 1):

- Flow rates (30, 60 and 100 L/min)
- Storage conditions (4 h at 40°C 75% RH) to simulate patient misuse (e.g. exhalation) or inappropriate storage in a warm humid environment.

Several investigations have shown that the capsule plays an important part in delivery from capsule-based DPIs, because not only does it participate as packaging of the formulation, but it also has a role in the aerosolisation of the powder and the dispersion of the micronised drug from the carrier after the patient has pierced the capsule and inhaled through the DPI.¹³

The two hard capsule types currently available in the pharma market are firstly the gelatin capsule, used as the pharmaceutical standard for more than 100 years, and secondly the HPMC capsule that has risen to the fore in recent years. HPMC has increased in popularity following a significant amount of pharmaceutical research showing that gelatin capsules are not suitable for encapsulating hygroscopic products, and are chemically unstable under certain conditions. HPMC capsules have emerged in the market as the most viable alternative because of their vegetal origin, chemical stability, absence of crosslinking and low moisture content (4.5-6.5%).

Within the framework of this study, the drug retention in the different types of capsule – Quali-V[®]-I manufactured by Qualicaps[®], and Vcaps[®] / Vcaps[®] Plus manufactured by Capsugel[®] (Morristown, NJ, US) – was evaluated together with the fine particle dose (FPD \leq 5 µm) expected to deposit in the peripheral part of the lungs (see Figure 1). A low resistance device, Axahaler[®] (SMB, Brussels, Belgium) was used connected to a Next Generation Impactor (NGI; Copley Scientific, Nottingham, UK).

The main conclusions of the investigation can be summarised as follows:

- At the optimal flow rate (100 L/min) the FPD was higher for HPMC capsules (Quali-V[®]-I and Vcaps[®]) in relation to gelatin capsules and the 2nd generation HPMC capsules (Vcaps[®] Plus).
- At the different flow rates corresponding to 30, 60 and 100 L/min, only the HPMC capsules (Quali-V[®]-I and Vcaps[®]) presented no differences in the FPD between 60 and 100 L/min. Therefore, more robust performances were observed with HPMC *versus* gelatin capsules that could be explained by the higher moisture content inherent in gelatin capsules (13-16% *versus* 4.5-6.5% for gelatin and HPMC capsules, respectively).
- The drug retention in the capsules at 100 L/min was lower in HPMC capsules (Quali-V®-I and Vcaps®) than in gelatin capsules and the 2nd generation HPMC capsules (Vcaps® Plus). Additionally, Quali-V®-I showed the lowest formoterol retention in the capsule at the different flow rates.

It is well known that the patient can generate different flow rates through his/her inhalation device relating to its resistance. The differences in device resistance could result in various clinically relevant PIFR. Therefore, an alternative delivery device should be taken into consideration if patients have a pulmonary impairment and are unable to generate the optimum pressure drop or peak IFR.

Additionally, it is important that the combination of the dry powder for inhalation and its capsules present high FPD with low dependency on a flow rate (between 60 and 100 L/min) and low capsule retention. HPMC capsules showed higher and more robust FPD at this flow rate range than gelatin capsules, in particular Quali-V[®]-I with the lowest capsule retention at all tested flow rates. However, it is very important to avoid exposing the capsules to adverse conditions, which could affect significantly the aerodynamic performance of dry powder, regardless of the kind of capsules used.

CONCLUSION

The delivery of respiratory drugs via capsule-based DPIs offers an environmentally friendly alternative, as these devices enable the possibility of reducing a major source of greenhouse emissions over the years. The gradual transition is aligned as well with the new Rigali climate summit measures decided and agreed recently this year by almost 200 countries worldwide.

As presented in this article, both types of inhalation delivery system – capsule-based DPIs and pMDIs – are considered to be equally effective, so an expected acceptable clinical outcome for patients is ensured.

On the other hand, capsule-based DPIs are breath-actuated devices and avoid the often low and variable lung dose resulting from poor pMDI handling techniques.

The capsule behaves as the primary packaging material for the drug formulation

and is considered an important part of the inhalation system because it participates in the aerosolisation of the powder and the dispersion of the micronized drug from the carrier after piercing the capsule. HPMC capsules have been shown to produce improved results compared with gelatin capsules with regard to the FPD and drug powder retention in the capsule.

Finally, the general ecological and sound scientific approach of capsule-based DPIs is in line with patient preferences. Nevertheless, it is in the hands of clinicians and policy makers to implement the adequate changes and to properly inform patients in order to consider switching to this more sustainable option.

REFERENCES

- Okamura S, Ashford P, Jackson J, Watterson J, "HFC consumption and emissions forecasting". Report to UK Department for Environment, Food & Rural Affairs (prepared by AEA Technology PLC), 2011.
- 2. United Nations Environmental Program (UNEP) News Centre
- 3. Hillman T, Mortimer F, Hopkinson N, "Inhaled drugs and global warming: time to shift to dry powder inhalers". BMJ, 2013, Vol 346, f3359.
- Velders et al, "Future atmospheric abundances and climate forcings from scenarios of global and regional hydrofluorocarbon (HFC) emissions". Atmospheric Environment, 2015, Vol 122, pp 200-209.
- UK National Institute for Health and Clinical Excellence (NICE) Clinical Guideline, "Chronic Obstructive Pulmonary Disease. Costing report implementing NICE guidance". February 2011. (Available at: https:// www.nice.org.uk/guidance/cg101/ resources/costing-report-134511805)
- 6. Dolovich MB, Ahrens RC, Hess DR, Anderson P, Dhand R, Rau JL,

et al, "Device selection and outcomes of aerosol therapy: evidence-based guidelines". Chest, 2005, Vol 127, pp 335-371.

- 7. Shepherd J, Rogers G, Anderson R, Main C, Thompson-Coon J, Hartwell D, et al, "Systematic review and economic analysis of the comparative effectiveness of different inhaled corticosteroids and their usage with long-acting beta2 agonists for the treatment of chronic asthma in adults and children aged 12 years and over". Health Technol Assess, 2008, Vol12(iii-iv), pp 1- 360.
- Borgström et al, "Degree of throat deposition can explain the variability in lung deposition of inhaled drugs". J Aerosol Med, 2006, Vol 19, pp 473-483.
- Al-Showair et al, "Can all patients with COPD use the correct inhalation flow with all inhalers and does training help?"Respir Med, 2007, Vol 101, pp 2395-2401.
- Chavan V, Dalby R, "Effect on rise in simulated inspiratory flow rate and carrier particle size on powder emptying from dry powder inhalers". AAPS Pharm Sci, 2000, Vol 2, E10 [Abstract].
- 11. Borgström L, "On the use of dry powder inhalers in situations perceived as constrained". J Aerosol Med,2001, Vol 14, pp 281-287.
- Wauthoz N, "Influence of Flow Rate and Usage in Drastic Condition on the Aerodynamic Performance of a Formoterol Dry Powder Formulation using different kinds of capsule". Abstract at AAPS Annual Meeting, 2016 (Denver, CO, US).
- Coates MS, Fletcher DF, Chan HK, Paper JA, "The role of capsule on the performance of a dry powder inhaler using computational and experimental analyses". Pharm Res, 2005, Vol 22(6), pp 923-932.



UNPARALLELED TIGHT TOPIC FOCUS, EVERY ISSUE, FOR OVER A DECADE www.ondrugdelivery.com

ntble®

PATIENT PREFERENCE OF RESPIRATORY DEVICE TRAINING & EDUCATIONAL TOOLS

Although pulmonary delivery is a popular and growing method of drug delivery, evidence shows that most patients with asthma do not use their inhaler properly. Paul Sullivan, Associate Director, Business Development, and Craig Baker, Executive Vice-President, from Noble, review the evidence from a trial of five different methods and conclude that training devices could be effective tools to increase patient confidence and reduce anxiety.

Pulmonary drug delivery is an effective route of administration for localised and systematic uptake of pharmaceutical products. As a result, pulmonary administration is a viable alternative to more invasive routes, with future growth potential across new therapeutic areas. These products are often marketed as combination therapies, consisting of active pharmaceutical ingredients and drug delivery devices. When properly used by patients, these devices administer a prescribed dose to the lungs.

"According to a recent study published by the American College of Allergy, Asthma and Immunology, only 7% of inhaler patients follow the proper technique when using their devices."

Over the years, the use of pulmonary drug administration has continued to grow, with more patients being introduced to pulmonary delivery devices such as metered dose inhalers (MDIs), dry powder inhalers (DPIs) and nebulisers. Healthcare professionals receive professional training on the correct ways to use delivery devices, but when the patient, who has limited to no experience, receives in-office training on how to use the device, it's often not memorable or fully understood, resulting in misuse at home. According to a recent study published by the American College of Allergy, Asthma and Immunology, only 7% of inhaler patients follow the proper technique when using their devices.

"Recent publications have confirmed that most patients with asthma do not use their inhaler properly. In addition to only 7% of users demonstrating perfect technique, 63% failed to complete three or more steps. This is a good reason for much needed education, both verbally and visually, to be administered by physicians and asthma educators," said Dr Sam Pejham, Assistant Clinical Professor at University of California at San Francisco (UCSF) School of Medicine.

"Also the availability of trainers for patients to demonstrate in front of their provider how they use their inhaler is crucial to ensure proper technique. Currently, asthma patients' poor inhaler technique is causing them to have diminished drug delivery which could lead to poor asthma management."

One important factor in recognising



Mr Paul Sullivan Associate Director, Business Development T: +1 888 933 5646



Mr Craig Baker Executive Vice-President

Noble

121 South Orange Avenue Suite 1070 North Orlando, FL 32801 United States

www.gonoble.com

"Improving the training process for pulmonary drug administration is a key opportunity for pharmaceutical brands."

patient centricity is the first 30, 60, or 90 days after diagnosis, commonly called onboarding – this is the time when patients are first introduced and trained on how to use drug delivery devices. In-office training is undoubtedly vital and beneficial. However, inconsistencies in training technique and various environmental conditions can affect this training and cause deviations within patient groups.

Improving the training process for pulmonary drug administration is a key opportunity for pharmaceutical brands. Noble, the leader in design and manufacturing of multisensory drug delivery training devices, identified deviations and inconsistencies as an unmet clinical and market need. The company conducted an in-depth analysis of secondary literature to understand causes of product misuse and developed strategies that could be implemented to improve patient adherence and outcomes. A study was also conducted to understand the impact of various forms of training materials and devices on patient performance.

Having identified user error as a significant risk factor, a review of commercial device platforms and instructions for use (IFU) was conducted to understand common usage steps and the source of errors during the administration sequence. Figure 1 is a summary of common tasks associated with the use of an MDI. Included is a preliminary risk level assessment correlating the severity, detectability and probability of errors in common usage steps.

STEP	DESCRIPTION	RISK OF ERROR	FREQUENCY OF ERROR
1	Prepare device	Low	Low
2	Remove mouthpiece	Low	Low
3	Inspect mouthpiece and device	Medium	High
4	Prepare device and dose (i.e. shake, prime, etc.)	High	High
5	Exhale fully	High	High
6	Place and properly orient device in mouth	Medium	Medium
7	Actuate device to deliver medication	High	Medium
8	Inhale with the appropriate force	High	High
9	Inhale at the appropriate sequence and duration	High	High
10	Hold breath for appropriate duration	High	Medium
11	Repeat as prescribed	High	Medium
12	Clean and store device as prescribed	Low	Medium

Figure 1: Common MDI instructions for use (IFU) steps. The most common errors are failure to prime, exhale and co-ordinate actuation with the necessary timing, force, and duration of the patient's inhalation. These factors commonly correlate with successful delivery, deposition and absorption of medication.



In a study, five training methods were analysed:

- Instructions for use (IFU) document: this is a traditional 12-step IFU, based on common themes and steps of currently marketed respiratory devices.
- Mechanical training device and IFU: a mechanical simulator of a currently marketed respiratory device was used. All forces, feedback and behaviour were accurately simulated.
- Training device calibrated whistle and IFU: the training device has a mechanical whistle calibrated to respiratory flow rate requirements of common inhalers.
- Training device with auditory instructions and IFU: a training device with auditory instructions walks patients through the IFU in a predetermined sequence.
- Smart training device for detecting errors and IFU: a training device with sensors and adaptive algorithms is used to detect and teach patients how to prevent errors (see Figure 2).

The study found that users are most confident when training and onboarding with smart training devices that detect and teach them how to prevent errors. Patient confidence is a significant driver of compliance and patient adherence. In light of the importance of confidence during onboarding, training device configurations were evaluated to determine how each affected patient confidence. Based on participants' feedback, 82% of users would feel most confident when training with a device that detects and corrects errors. Across all configurations, training devices



IN WHICH ISSUE SHOULD YOUR COMPANY APPEAR? www.ondrugdelivery.com

increased confidence by 41%, which is consistent with other device-related studies.

"For us, usability and human factors go hand-in-hand with effectively training patients to use our drug delivery devices," says Chris Evans, Vice-President of Research and Innovation at West Pharmaceutical Services (Exton, PA, US). "By instilling confidence with good training, fear or anxiety is eliminated when someone is injecting themselves or a loved one. It also eradicates some major barriers to adherence and compliance."

Similar to confidence, anxiety can result in stress and avoidance behaviours that adversely affect patients' adherence to therapy. Based on participants' feedback, 76% of users prefer error detection technologies to overcome anxiety when onboarding to device-delivered therapies. Patient anxiety decreased by 18% across all training methods evaluated during this study (Figure 3). Smart training devices with error-detecting technologies are preferred methods in overcoming anxiety and preventing errors.

In addition to evaluating the effects of training on confidence and anxiety, the study sought to understand the patients' overall training preferences and how these factors would relate to their ability to use a pulmonary delivery device safely and effectively. Figure 4 is a summary of these findings related to overall preferences and expected delivery outcomes. Users trained with smart, error-detecting technologies would make the fewest errors when administering with pulmonary delivery devices.

Based on a review of secondary literature, errors and technique are significant adherence barriers for patients



Figure 2: Preference (%) related to confidence when onboarding with specific training device configurations.



Figure 3: Preference (%) related to anxiety when onboarding with specific training device configurations.

using pulmonary delivery devices. The findings of this user study suggest that training devices could be effective tools to increase patient confidence and decrease anxiety – two variables that are closely associated with adherence and patient outcomes. Though the findings were robust and insightful, follow-up research is recommended to evaluate device training on actual patient errors and long-term outcomes further.

"With increasing self-administration of injectable medications, it is critical that we recognise the best drug and delivery



Figure 4: Users would make the fewest errors after being trained with error-detecting technologies (left). Users prefer errorcorrecting training when onboarding to pulmonary delivery devices (right). system is only effective if the patient delivers the dose correctly, and in accordance with the appropriate treatment regimen," says Graham Reynolds, Vice-President, Marketing and Communications, Pharmaceutical Delivery Systems at West Pharmaceutical Services.

"While manufacturers continually work to better understand user needs and design drug delivery systems for affinity, it is also imperative that we spend more time on effective training and onboarding for patients – with the aim of improving patient adherence and outcomes over the long run."

As pulmonary delivery markets continue to evolve, patients and industry stakeholders will continue searching for value and differentiation. At its core, the goal of device training is to fulfill such needs and support patients in the successful management of their treatments.

ABOUT THE AUTHORS

Paul Sullivan is the Associate Director of Business Development at Noble®, a product development company with a focus in designing and manufacturing drug delivery training and patient on-boarding solutions. Prior to Noble, Mr Sullivan worked at Informed Medical Communications, as a Director of Business Development and Client Service. His primary role was to train physician and nurse key opinion leaders on the skills of peer-to-peer influence and round-table moderating. In 2003, started his career in the pharmaceutical industry as a pharmaceutical sales representative with Procter & Gamble Pharmaceuticals and holds a Kinesiology degree with honors from the University of Western Ontario (Canada) and resides in Cincinnati, OH, US.

Craig Baker joined the company just a few years after its creation. Mr Baker holds an undergraduate degree from the University of Iowa and a Masters degree from University of South Carolina. In addition, he has 10 years of management experience in the marketing industry and the pharmaceutical & healthcare field. This unique insight into both industries is an important advantage for the future growth of Noble. ON drugDELIVERY

2017 EDITORIAL CALENDAR

Publication Month	Issue Topic	Materials Deadline
Jan 2017	Ophthalmic Drug Delivery	EXTENDED
Feb 2017	Prefilled Syringes	Dec 19th
March 2017	Skin Drug Delivery: Dermal, Transdermal & Microneedles	Jan 23rd
April 2017	Pulmonary & Nasal Drug Delivery	Feb 20th
May 2017	Injectable Drug Delivery: Devices Focus	March 20th
June 2017	Connected Drug Delivery Systems	April 17th
July 2017	Novel Oral Delivery Systems	May 22nd
Sept 2017	Wearable Injectors	July 24th
Oct 2017	Prefilled Syringes	Aug 21st
Nov 2017	Pulmonary & Nasal Drug Delivery	Sept 25th

Copyright © 2016 Frederick Furness Publishing Ltd





APRIL 25 - 28, 2017 Palais des Congrès d'Antibes Nice, FRANCE

DEADLINE: Scientific Poster Abstract Submission January 6, 2017

rddonline.com/rddeurope2017



RDD Europe is a conference jointly organized by



Aptar

VCU RDD Peter R. Byron Graduate Student Award All graduate student poster presenters attending RDD Europe 2017 are eligible. Details on conference website.







Quantum Dose Indicator System

Presspart, the world's leading manufacturer of metered-dose inhaler canisters and actuators, has developed the Quantum end of life indicator system for MDI's

Quantum has been developed to be a low cost, disposable MDI indicator solution, ensuring

patients don't run out of their medication when they need it most.

Quantum also now features an interactive mobile app for patients to use in conjunction with the Quantum system to track their medication usage, even if the patient uses multiple inhalers.

The Quantum logo is a registered trademark of Presspart Manufacturing Ltd



BICCORP

LEVERAGE TECHNOLOGY TO OVERCOME PULMONARY DRUG DELIVERY CHALLENGES

Here, Jean Vuillecard, Innovation & Product Manager, and Eric Dessertenne, Head of Business Development, both of Biocorp, define the limitations of traditional strategies to train, educate and track patient adherence with inhaled therapeutics and show how connectivity and other add-on digital technology can provide the support with these strategies that healthcare providers require.

THE LIMITS OF TRADITIONAL INHALED THERAPIES

Over the years, inhalation has been recognised as the main route of administration for asthma and chronic obstructive pulmonary disease (COPD) treatments, being preferred to oral medication. Indeed, inhaled medication allows high concentration and localised drug delivery leading to direct pharmacological effects while having lower risk for systemic side effects.

However, despite proven results in terms of clinical efficacy, delivery of inhalation drugs appears to be more complex than oral drugs. Where swallowing tablets is sufficient to achieve the desired therapeutic outcome, the effectiveness of an inhaled therapeutic is heavily dependent on the

"When connected with a pMDI, Inspair is capable of tracking every inhalation directly from the patient's inhaler. Specific sensors capture unique data related to breath-hand co-ordination, inhalation speed/depth and inhaled dose." drug formulation, user-friendliness of device design, and patient ability to inhale the right amount of active substance. Pulmonary drug delivery devices have to master all these aspects before achieving the desired therapeutic goals.

Medical device companies have developed a wide range of inhalers with brilliant designs and innovative mechanisms over the past few decades. For drug dissolved in a propellant, suspended into droplets or in dry powder, the number of inhaler designs has greatly increased over the last decades. Today, dry-powder inhalers (DPIs) and metered-dose inhalers (MDIs) are the main devices prescribed for asthma and COPD. Due to a relative low cost per dose, MDIs are still widely used and far ahead DPIs in terms of volume. However, evidence from published scientific literature demonstrates that the clinical effectiveness of an inhaler is closely dependent on the patient's inhalation technique.1

Regardless of inhaler devices used, symptom control observed among European patients is suboptimal in 56.5% of the patients with asthma. This low proportion achieving symptom control is associated with a decline in quality of life, higher risk of exacerbations, and greater consumption of healthcare resources.² According to LIAISON (the largest observational studies on characteristics and management of asthmatics in Europe), low adherence to therapy and insufficient training of patients in the appropriate inhalation techniques



Jean Vuillecard Innovation & Product Manager T: +33 688 697 285 E: ivuillecard@biocorp.fr



Eric Dessertenne Head of Commercial Operations & Business Development T: +33 608 021 451 E: edessertenne@biocorp.fr

BioCorp

Parc Technologique Lavaur-La-Bèchade 63500 Issoire France

www.biocorpsys.com

are amongst the most important factors contributing to uncontrolled asthma.

For most long-term treatments, keeping patients compliant with the initial prescription is a key challenge. Indeed, poor adherence to treatment leads to uncontrolled symptoms and, as a consequence to a degradation of patients' quality of life. However, understanding the causes of non-adherence is tricky since a number of medication-related and non-related factors are associated with patients' ability and willingness to stick to their inhaled therapy.

Poor adherence is associated with a higher risk of symptom exacerbation and it is therefore critical to identify treatmentrelated issues at early stages. Too often, the over-consumption of rescue medication reveals suboptimal asthma control arising from poor adherence to longterm controller medications. Meanwhile traditional self-reporting methods are not reliable and "white coat" compliance could be misleading for healthcare professionals (HCPs). Despite dose-counters being integrated into inhalers, identifying patients who are slowly drifting away from inhaled therapy is a complex mission. For instance, an often confusing situation appears when patients believe they are taking medications as prescribed but, in reality, unintentionally use inhalers the wrong way. Inhalation errors have been well documented in the medical literature and seem to have a direct impact on intended therapeutic goals.

As pointed out by the Guide for Asthma Management and Prevention 2015, more than 80% of patients living with asthma do not use their inhaler adequately. Even more disturbing, a recent audit among HCPs³ confirmed previously published studies stating less than 10% of HCPs were competent for advising patients on the best use practices of MDIs.⁴ Data (see Figure 1) indicate that the most frequent errors when using an MDI are:

- the lack of breath-hand co-ordination (45%)
- speed and/or depth of inspiration (44%)
- no-post inhalation breath-hold (46%).⁵

Inadequate education of patients in inhalation techniques is too frequent and systematic reviews question this situation,



Figure 2: Duration of device use versus error, comparison. (Source: Arora, et al 2014)

which has not changed significantly over the last 40 years, though considerable effort has been invested in education, training and device development.⁵

LEVERAGE TECHNOLOGY TO OPTIMISE TREATMENT OUTCOMES

Given these observations, we should rethink the way inhaled therapies are provided to patients. Despite medical guidelines aiming to reduce non-adherence and inhaler misuses, patients and their caregivers should be provided with user-friendly and highquality educational material to improve the way they use their inhalation devices. As described by Gilette *et al*, inhalation techniques are significantly improved after educational interventions, especially in paediatric patients.⁶

HCPs are the most appropriate people to provide such instructions and to correct mistakes when made in order to ensure effective drug therapy and delivery; but this process is long and time-consuming. This is where technology can really support HCPs, identifying patients requiring specific (re)training and providing precious help to improve adherence to therapy and inhalation techniques over time.

During medical appointments, patients often have difficulty sharing and describing treatment-related issues and discomfort. Identifying handling inhalation errors made at home is not an easy task, since patients try to do their best and will try to minimise their mistakes when in front of HCPs. People living with asthma can be advised to keep a logbook with daily doses inhaled (preventer and reliever medication), symptom frequency as well as exposure to triggers. However, very few have the time and motivation needed to keep such a diary over the years. In many cases, daily habits make it difficult to remember medication over-consumption or forgotten doses.

So HCPs are still lacking information regarding patients' day-to-day adherence and inhalation techniques. Furthermore, a steep increase in the number of errors within patient groups using a device for more than two years has been clearly described (see Figure 2). Therefore, patient education should be provided over the whole period inhaled therapy is being used, and re-training patients using inhalers for long periods should also be considered.

To overcome these challenges, Biocorp designed Inspair – a smart solution collecting data related to treatment adherence and

inhalation techniques. In addition to reconnecting patients with doctors, Inspair functionalities foster better self-care therapy.

Inspair consists of a smart sensor that can be attached to any pMDI (see Figure 3). Connected with a dedicated mobile app via Bluetooth, the smart solution embeds an inhalation tracking system, an active feedback system as well as digital features to allow treatment monitoring.

"Inspair's solution offers a range of digital tools to improve traditional treatment monitoring. From inhaled dose and symptom logbooks to seasonal triggers, Inspair's electronic reports can be personalised and enriched with environmental exposure and symptom control insights."

INHALATION TRACKING SYSTEM

When connected with a pMDI, Inspair is capable of tracking every inhalation directly from the patient's inhaler. Specific sensors capture unique data related to breath-hand co-ordination, inhalation speed/depth and inhaled dose.

Dose counting is definitively a useful feature but all the doses counted are not necessarily doses that were inhaled by the patient. Knowing the difference is critical to identifying the root causes of suboptimal treatment outcomes when patients seem to comply with the prescribed therapy.

Physicians and patients need more information on the inhalation itself to make better decisions. Having access to accurate and objective metrics offers new possibilities as to how to manage long-term therapy and encourage patient self-improvement.

ACTIVE FEEDBACK & EDUCATIONAL SYSTEM

Pulmonary drug delivery using pMDIs requires patients to follow complex handling instructions with several operations to be performed in a specific sequence. The correct inhalation manoeuvre turns out to be complicated for patients, particularly for children and the elderly.

To reduce the complexity of using pMDI, Inspair embeds visual and audio signals providing guidance throughout the inhalation process. From inhaler shaking to the breathhold step, patients receive a clear and userfriendly guide through the inhalation.

Inhalation data are then automatically recorded and transmitted to a dedicated mobile app. A feedback system points out both correct use and misuse. Based on personal inhalation data, the app provides useful advice to the patient to improve inhalation technique and therefore optimise drug delivery and treatment outcomes.

Inspair's active feedback system is a digital, personalised educational tool acting like a coach. Its ultimate objective is to support patients and HCPs at every stage of inhaled therapies.

DIGITAL FEATURES TO MONITOR INHALED THERAPY

When it comes to long-term therapy, having access to comprehensive and accurate treatment data is critical for effective monitoring. Now with the support of technology, patients, caregivers and HCPs are able to monitor inhaled therapy as never possible before.

Inspair's solution offers a range of digital tools to improve traditional treatment monitoring. From inhaled dose and symptom



logbooks to seasonal triggers, Inspair's electronic reports can be personalised and enriched with environmental exposure and symptom control insights. These digital features provide patients and HCPs with a clear view of the treatment with real-life, day-to-day information.

An alert feature allows relatives, caregivers



Figure 4: Handling error rates among patients who switch inhalers.⁷

or HCPs to be informed about lack of adherence, overexposure, and potential triggers and symptom exacerbations.

ADD-ON APPROACH: SEAMLESS INTEGRATION OF TECHNOLOGY

The wide adoption of information technology into healthcare is transforming drug delivery and monitoring. Patients are demanding modern and more effective health services. Consequently, medical devices are taking advantage of digital features and wireless connectivity to optimise traditional treatment outcomes. The medical device sector cannot stop innovating and our objective is to continue bringing new technologies that will improve patient therapy and safety. However, we should be careful that innovations do confuse patients and HCPs.

Jumping directly to a completely new inhaler devices with high-tech features embedded could achieve the opposite of what innovation is aiming at – improving medication delivery and patient's experience safety. Leiner *et al* provide a well-documented body of evidence on the consequences of switching inhaler devices.⁷ Figure 4 points out the increasing error rates among patients switching from one inhaler to another. It is therefore important that patients can keep using the same inhaler when appropriate. As medical device developers we focused on developing a way to integrate technology seamlessly into the current patient environment. The add-on approach appears to be the best solution to turn existing devices into smart inhalers without dramatically changing the patient's familiar routine.

"Inspair's add-on does not require the initiation of a new inhaler device development program. Fully customisable and cost-effective, Inspair's smart sensor can be adapted to suit every pMDI available on the market."

Inspair is a compact add-on module designed to fit MDIs without interfering with spray diffusion (see Figure 5). That way, patients can continue to use their inhaler as usual. This add-on approach enhances treatment management possibilities while avoiding the confusion that can arise from having to use an entirely new inhaler.

Another distinct advantage of the add-on approach is that, in terms of

time-to-market, add-on is the fastest way to bring addedvalue products to patients and to HCPs. Indeed, Inspair's add-on does not require the initiation of a

new inhaler device development program. Fully customisable and costeffective, Inspair's smart sensor can be adapted to suit every pMDI available on the market.

In addition, the add-on approach is durable. When inhalers are empty, patients throw them away. As the Inspair smart sensor is removable and reusable, patients can continue to use it with new devices. It allows patients to keep track of inhalations over longer periods.

CONCLUSION

Pulmonary delivery is a highly effective administration route for respiratory disease treatments. However, suboptimal outcomes have been observed in an increasing part of patients living with asthma and COPD. Despite efficient medical devices, patients still struggle to use inhalers in line with recommendations. Low adherence and incorrect inhalation techniques have a significant impact on patient quality of life and symptom exacerbation. Numerous studies have pointed out the lack of proper training among patients and HCPs.

For these reasons, Biocorp has developed Inspair, a connected solution turning any traditional inhaler on the market into a smart device. Inspair is a compact, add-on module designed to fit pMDIs without interfering with spray diffusion. Smart sensors collect unique inhalation data and are connected to smartphones via Bluetooth low energy. This innovative solution offers new possibilities for improving the education of patients and HCPs in the most appropriated way to use inhalers and to enhance patient adherence.

REFERENCES

- 1. Brocklebank D et al, "Comparison of the effectiveness of inhaler devices in asthma and chronic obstructive airways disease: a systematic review of the literature". Health Technol Assess, 2001, Vol 5(26), pp 1-149.
- Braido et al, "Determinants and impact of suboptimal asthma control in Europe", Respiratory Res, 2016, Vol 17(1), pp 51.
- Goodwin R et al, "Inhaler counselling, the real deal of just fresh air?" Arch Dis Child, 2016, Vol 101(9), p e2.
- Baverstock M et al, "Do healthcare professional have sufficient knowledge of inhaler techniques in order to educate their patients effectively in their use?" Thorax, 2010, Vol 65, pp A117-A118.
- 5. Sanchis J et al, "Systematic Review of Errors in Inhaler Use: Has Patient Technique Improved Over Time?" Chest, 2016, Vol 150(2), pp 394-406.
- 6. Gilette C et al., "Inhaler Technique in Children with Asthma: A Systematic Review". Acad Pediatr, 2016, Vol 16(7), pp 605-615.
- Leiner S et al, "Inhalation devices and patient interface: human factors". AAPS J, 2015, Vol 17(2), pp 457-461.

Figure 5: Inspair fits pMDIs without interfering with spray diffusion.

BIOCORP, YOUR TRUSTED PARTNER FOR INTEGRATED TREATMENT SOLUTIONS



BEYOND TREATMENT

+33 (0)6 08 02 14 51 edessertenne@biocorp.fr



2,1

52

ays

available on the market

INSPAIR, A SOLUTION TO MONITOR MDI USE

Nemera

ADVANCIA®: A TRUE PLATFORM & INNOVATIVE SYSTEM OFFERING EFFICIENT NASAL DOSE DELIVERY

Millions of people suffering from allergic rhinitis use nasal sprays manufactured by Nemera every day. In this article, company Global Category Manager, ENT Products, Pascale Farjas, provides an overview of the company's nasal delivery platform, Advancia[®].

"Because the efficacy of the drug depends upon the spray device's ability to deliver a uniform dose as well as a reproducible droplet size and plume, the delivery system is a critical element for nasal spray performance."

The intranasal route is widely used both for prescription and over-the-counter (OTC) drugs. It is an attractive option for locally acting / topical drugs (e.g. nasal decongestants or nasal steroids), as well as for systemic acting drugs (anti-migraine medication, hormones, etc), boasts a rapid onset of action and it is very convenient.

Because the efficacy of the drug depends upon the spray device's ability to deliver a uniform dose as well as a reproducible droplet size and plume, the delivery system is a critical element for nasal spray performance.

Moreover, treatments via the nasal route are self-administered and therefore nasal delivery systems have a positive impact on compliance. Patients should be able to rely on their nasal spray anytime during the treatment, especially during allergy-related symptoms. That's why the device must be user-friendly and convenient to carry around.

Nemera offers standard delivery devices for nasal, buccal and auricular routes for both OTC and prescription drugs. They are recognised and valued by patients and pharmaceutical companies alike. The company guarantees precision and dose consistency, to ensure an optimal treatment.

The development of the multidose nasal spray, Advancia[®], illustrates perfectly Nemera's patient-oriented innovation process. The new technology pump provides outstanding performance responding to increasing regulatory requirements for nasal sprays.

Advancia[®] (see Figure 1), is the high performing metering pump platform that patients can count on. With accurate dosing, patients can be confident that each dose is fully delivered. Advancia[®] offers an alternative to improve treatment compliance in an increasingly demanding nasal spray market. Designed to be a step ahead of today's pumps, Advancia[®] is based on a new system combining user-independence and preservative-free features in one single system.

A TRUE PLATFORM

Advancia[®] is offered in various different configurations (two pump engines, two fitments, three doses), making it a true nasal drug delivery platform suitable for:

- Lifecycle management of off-patent allergic rhinitis products and OTC decongestants
- New combination treatments that target nasal allergies (e.g. steroids + antihistamines)
- Pipeline allergy molecules

www.ondrugdelivery.com

• New drugs in development through the nasal route.

Advancia[®] Crimp-on is covered in a US DMF Type III.



Pascale Farjas Global Category Manager ENT Products T: +33 4 74 94 92 94 F: +33 4 74 94 90 60 E: pascale.farjas@nemera.net

Nemera

20, Avenue de la Gare 38290 La Verpillière France

www.nemera.net

Nemera

PATENTED ANTI-CLOGGING ACTUATOR

The Advancia[®] platform's closing tip prevents clogging, which can be a particular problem with formulations prone to crystallisation. The patented closing tip mechanism (shown in Figure 2):

- 1. Ensures that no contamination can enter through the actuator orifice
- 2. Provides protection from crystallisation and clogging issues
- 3. Avoids evaporation to guarantee excellent prime retention.

This benefit improves patient compliance and can drastically reduce the number of complaints due to non-functioning pumps.

Other key product features of Advancia® include:

- User-independence
- Excellent dose consistency
- Long prime retention
- Mechanical closing tip to prevent clogging issues
- No metal part in contact with the formulation
- Plastic components made of polyolefins only (PE and PP) which comply with EP-USP-FDA regulations
- DMF available
- One-step snap-on process to boost productivity on filling lines.

Example specifications for different configurations of Advancia[®] are summarised in Table 1.

USER STUDIES

The patients' voice is the key driver of all Nemera product development. Patient insights and human factors studies are at the heart of the innovation process. We conduct user studies to make sure our products respond to patient needs, and to benchmark Nemera delivery systems *versus* competition. Two user studies were performed with Advancia® in 2011 and 2013 with 30 patients, including children, adults and seniors, with a double objective:

- Demonstrate the user-independence feature of Advancia®
- Benchmarck Advancia[®] against competition on dose consistency.



Figure 2: The patented closing tip mechanism that prevents clogging.

	Advancia® Std	Advancia® PF*
Eitmont	Crimp-on 20 mm	Snap-on 20 mm
Fitment	Snap-on 20 mm*	
Doses (µl)	50, 100, 140*	50, 100, 140*
Raw materials in contact with the formulation	PE, PP, gasket raw materials, silicone	PE, PP, silicone
Nacal actuators	Crimp-on: AI	05701
Nasai actuators	Snap-on: AD	5705

* in development

Table 1: Specifications of different Advancia configurations.

Comparison with Competitor Pumps

Regardless of the design, the reproducibility of the dose is one of the most crucial attributes as this parameter may affect the delivery of the drug substance to the intended biological target. As shown in Figure 3, Advancia® is the best performing pump, both on dose adjusting versus nominal value and reproducibility, independently of the user. As a reminder, pump spray weight delivery acceptance criteria should control the weight of the individual sprays to within 15% of the target weight and their mean weight to within 10% of the target weight.

Because of user-independence feature, the activation speed is higher for Advancia[®] than for other pumps (illustrated by white diamonds on the graph in Figure 3). This is a specific and patented design. This feature is achieved with a commitment point, designed to accumulate energy at the beginning of the stroke. As a consequence, the user cannot stop the pump actuation before the end of the stroke and will have a full dose delivered.

Designed with Users' Real Lives in Mind Patient feedback from the user studies was also collected on Advancia[®] Snap-



Figure 3: Comparison of dose accuracy and speed of actuation from Advancia® with competitor devices.

on and four competitor devices. While the competitor devices look alike, Advancia[®] Snap-on was perceived to have outstanding style and usage features. Users highlighted its "all-inclusive design", perfectly adapted to real life situations where users carry their drug with them. The sleek, all integrated design of Advancia[®] makes it less prone to

"In early 2017, a preservative-free version of Advancia® Snap-On version will be available for customer sampling."



Figure 4: Advancia's design means it is an easy-to-fill system with one-step assembly.

accumulating dirt in a bag or a pocket, whereas the overcap makes it easier to manipulate and less prone to getting lost than the classic small caps present on other devices. Moreover, the actuator is designed to be ergonomically sound for all users including children.

In summary, Advancia[®] was shown to be the best performing pump, both on dose accuracy and reproducibility, independently of the user. Users also highlighted Advancia[®]'s integrated Snapon design, well-suited to today's on-the-go lifestyle.

EASY TO FILL, ONE-STEP ASSEMBLY

The design of Advancia[®] allows for a simple, efficient process during product filling and assembly (Figure 4). In terms of production, the main advantages of the Advancia[®] Snap-on system compared with competitors' devices are:

• No radial stress on bottle neck avoiding risk of glass bottles breakage or plastic bottles deformation or damage

- Sealing at the beginning of assembly process avoiding presence of foreign particles in the bottle due to friction between parts
- "Tamper Evident": very difficult to remove the system & not easy to re-place the actuator correctly onto the bottle
- Similar assembly force profile whatever the bottle is (material, neck design, etc).

Indeed, the assembly force required to snap the Advancia[®] system onto the bottle is very similar from one bottle to another, as opposed to standard snap-on systems where the bottle neck design can have a high impact on the assembly force profile.

ADVANCIA® CRIMP-ON: AVAILABLE NOW!

Nemera invested more than €10 million in Advancia[®]. A new European ISO8 clean room building with new injection moulding and assembly machines was constructed, with a focus on safety and quality with 100% tolerance controls and visual inspection on critical areas. As such, the next-generation nasal spray pump, Advancia[®], is now in production with annual capacity of 45 million units after full ramp-up...

... and in early 2017, a preservative-free version of Advancia[®] Snap-On version will be available for customer sampling.

ABOUT THE COMPANY

Nemera is a world leader in the design, development and manufacturing of drug delivery solutions. It has more than 50 engineers working in development, over 30000 m² of clean-room manufacturing, sales in 47 countries, 750 million+ devices produced yearly and over 1300 employees. Nemera has four plants in Europe and the US at Neuenburg, Germany; La Verpillière, France (Figure 5); Le Tréport, France; and Buffalo Grove, IL, US.

Nemera's portfolio includes devices across the board of drug delivery routes including parenteral; pulmonary; transdermal; buccal / auricular; and ophthalmic. This is in addition to the nasal offering described here.



Figure 5: Nemera's Innovation Centre at La Verpillière, near Lyon, France.



EXHIBITION & CONFERENCE 1 & 2 FEBRUARY 2017 PARIS EXPO, PORTE DE VERSAILLES, HALL 4

Pharma's dedicated packaging & drug delivery event



INNOVATION

NEW: Pharmapack Start-up Hub Pharmapack Awards Innovation Gallery Innovation Tours



NETWORKING

International Meetings Programme Exhibitor & Visitor Cocktail Party Networking Areas



EDUCATION

Conference Learning Lab Symposium Workshops



FREE TO ATTEND REGISTER NOW!

Follow the link: bit.ly/2bUPpR3



NEWS, WHITEPAPERS & EVENT PROGRAMME ON WWW.PHARMAPACKEUROPE.COM



Nemera



nasal/ buccal/ auricular



pulmonary



dermal/ transdermal



parenteral



SP270

Advancia®

0

SP270 PUMP PLATFORM FOR **ENT SOLUTIONS AND SUSPENSIONS** AND **ADVANCIA NEW USER INDEPENDENT NASAL SPRAY PLATFORM**

Nemera provides solutions for the pharmaceutical industry, including standard innovative products, development of custom devices and contract manufacturing.



Hovione Technology

A HovioneVentures company

SCALING UP FOR HIGH DOSE DELIVERY TO THE LUNGS

The interest in high dose compound delivery to the lungs is growing and driving the development of dry powder inhalers with enhanced dose delivery capability, in the range of 100 mg or more of active ingredient. In this article, João Ventura Fernandes, PhD, Business Development Manager; Gonçalo Rebelo de Andrade, PhD, MBA, Director; and Peter Villax, Chief Executive Officer, all of Hovione Technology, describe the scaling up of the currently marketed TwinCaps[®] inhaler into the new TwinMaxTM design for high-dose delivery of challenging drug-alone formulations in single to short-term treatments and emergency situations.

The use of dry powder inhalers (DPIs) is expanding beyond asthma and chronic obstructive disease (COPD) into new therapeutic targets that include pulmonary arterial hypertension, idiopathic pulmonary fibrosis, anti-emetics, anti-diabetic, antivirals and orally inhaled vaccines and antibiotics. Recent product launches together with the noticeably strong DPI pipeline on the non-asthma, non-COPD market¹ provide evidence of this expansion.

The growing interest in delivering anti-virals, antibiotics, vaccines, peptides or other drugs systemically via the lung in a single or a short-term treatment, has fueled the development of inhalers which comprise:

- A prefilled unit dose of powder for therapeutic benefit and convenience of use
- Are disposable for reasons of safety and hygiene
- Result in an economically viable product.

In addition, single-use disposable DPIs provide an attractive replacement alternative to the present use of multi-dose inhaler devices in emergency and hospitalisation situations, by providing the dose that is needed, instead of multiple doses the majority of which will remain unused. The economic benefit is therefore significant.

THE TWINCAPS® DPI

In 2006, Hovione began to develop a new DPI to deliver a long-acting neuraminidase

"The interest in delivering high dose compounds to the lung, in the range of 100 mg or more of active ingredient, is driving the development of DPIs with enhanced dose delivery capability."

inhibitor for the treatment of influenza. The target was the administration of the anti-influenza drug under pandemic situations, without or with minimal medical supervision and to inhaler-naïve patients, which would not be re-used to prevent contamination through the inhaler. It was therefore highly advantageous to have a sufficiently economic DPI that would be used once and disposed of.

Moreover, the majority of patients being inhaler naïve, it was fundamental to make the inhaler extremely simple and with the lowest possible number of user steps, as the fewer the parts, the fewer the number of patient errors and the greater the acceptance and compliance.^{2,3}

The answer to this challenge was TwinCaps[®], a single-use disposable inhaler comprising only two plastic parts: a body and a shuttle. The shuttle is a moveable component with two prefilled powder doses held in place by the body, which also



Dr João Ventura Fernandes Business Development Manager T: +351 21 982 9184 E: jventura@hovionetechnology.com



Dr Gonçalo Rebelo de Andrade Director T: +351 21 984 7619

E: gandrade@hovionetechnology.com



Peter Villax Chief Executive Officer T: +351 21 982 9361 E: pvillax@hovionetechnology.com

Hovione Technology Ltd

Loughbeg Ringaskiddy County Cork Ireland

Lisbon office: Estrada do Paço do Lumiar, Campus do Lumiar, Edifício R 1649-038 Lisboa – Portugal

www.hovionetechnology.com





Figure 1: Using TwinCaps[®]. In storage, the shuttle is leak-proof. In use, the patient removes the inhaler from a foil protective pouch, pushes the shuttle to the inhalation position and inhales. The process is repeated for the second dose. The total dose is thus divided into two smaller doses.

provides the mouthpiece. In use, the patient simply slides the shuttle from the storage position to the inhalation position and inhales, as shown in Figure 1, repeating the operation for the second dose. The device is then discarded.

EFFECTIVE & GRADUAL DELIVERY

An important innovation in TwinCaps[®] was the successful leak-proof containment of the powder dose inside the shuttle compartments, without resorting to film strips or foils, which add to complexity in manufacturing. This is achieved through a close fit between the body and the shuttle while ensuring a smooth sliding movement, which even elderly patients or patients with dexterity difficulties can operate.

In addition to powder containment and storage function, the prefilled shuttle compartment is turned into a dispersion engine once the patient pushes it into the inhalation position. This is a second key innovation in TwinCaps®. Making use of the power of Computational Fluid Dynamics (CFD) in inhaler design,4,5 Figure 2 shows that the compartment design creates a strong bottom jet featuring high turbulent kinetic energy that acts as a primary powder dispersion mechanism. An effective dispersion further assisted is by significant recirculation zones arising from the jet expansion through the restricted compartment

design. Such flow recirculation additionally contributes to increasing the particle residence time, which is beneficial to a gradual dose delivery to the patient during inhalation.

TwinCaps[®] was launched in Japan in 2010, as part of Daiichi Sankyo's Inavir[®] drug product. Its simple use, effective delivery and ease of manufacture brought commercial success and Inavir became the best-selling drug in the Japanese influenza treatment market and TwinCaps[®] the world's third largest-selling unit-dose inhaler.

A NEW CHALLENGE

In its original design, TwinCaps[®] was capable of delivering up to 20 mg of active drug per dose compartment, for a total of 40 mg per inhaler. However, orally inhaled antibiotics as well as new drugs in development require substantially higher payload capabilities – up to a total dose of 100 mg of active ingredient, or even more.

The high dose of active pharmaceutical ingredient (API) adds to the challenge - little air space is left inside the dose compartment for adequate dispersion and entrainment, leading to the need to reduce or eliminate flight-enhancing excipients to make more space for the active, and thus negatively affecting the potential for high dose delivery. This challenge needs to be addressed at formulation and inhaler levels. New particle engineering technologies, such as spray-drying, have enabled API-alone formulations, with the added benefit that even APIs which are chemically incompatible with known inhalation excipients can now be formulated and delivered.

Spray-drying is capable of generating improved control over particle size distribution and reproducibility, reducing amorphous content in crystalline product formulations and enhancing overall drug stability.⁶ Such particle engineered APIalone formulations are then normally characterised by high adhesion and cohesion properties resulting from the low median

Velocity Magnitude (m/s): 10 15 20 25 30 35 40 45 50

Figure 2: TwinCaps® CFD plot showing flow streamlines coloured by velocity magnitude.

Copyright © 2016 Frederick Furness Publishing Ltd

www.ondrugdelivery.com

particle size by volume, typically below 3 μ m, required for producing drug particles within the inhalable range.

The reduced delivery potential of highly cohesive and adhesive, high-dose, API-only formulations needs to be overcome by the aerodynamic efficiency of the inhaler. To deliver such challenging products, whether antibiotics, vaccines, proteins or peptides, powder inhalers need to be significantly more efficient. Taking TwinCaps[®] as the starting point, we initiated a development programme to scale-up its delivered dose.

FAST DEVELOPMENT

The development objectives specified keeping the same body-and-shuttle design, the same filling principle and the same actuation manoeuvre. Thus there was only the opportunity to work on and adapt the dispersion mechanism of the TwinCaps[®] inhaler to increase the drug payload by a factor of two to three times.

An accelerated inhaler development methodology was followed based on three steps:

- First, the generation of amorphous composite particles spray-dried out of a trehalose/leucine solution with median particle size by volume below 3 μm (Figure 3), and high cohesiveness and adhesiveness. These challenging particles model closely the behaviour of certain drug-alone formulations.
- Second, the rapid iterative development and prototyping of scaled-up TwinCaps[®] inhalers using 3D printing technology. This resulted in seven different models over the course of eight weeks of work and concentrated primarily on enhancing dispersion features in the device.
- Third, the rapid screening of the aerodynamic performance of each new inhaler configuration with the model particles, using a total dose of 80-100 mg and the gravimetric Fast Screening Impactor (FSI) testing for determination of the emitted mass (EM) and fine particle fraction (FPF).

SCALING UP DELIVERY

The first scaling-up iteration consisted of a simple linear increase in every TwinCaps[®] dimension, so as to accommodate a total dose of 80 mg with a bulk density in the range of 0.2-0.5 g/cm³. As shown in

PROTOTYPE	EM (%)	EM RSD (%)	FPF (%)	FPF RSD (%)
1. Scaled up TwinCaps®	53.9	16.7	54.9	12.3
2. Improved iteration	80.5	5.2	37.8	33.5
3. Improved iteration	85.7	1.7	40.6	1.0
4. Improved iteration	75.6	5.2	38.9	0.8
5. Improved iteration	88.5	4.3	28.7	2.1
6. Improved iteration	92.8	1.1	39.8	9.5
8. Final improvement	91.2	1.4	40.7	1.7

Table 1: Progress of delivery and deposition performance through seven TwinCaps[®] scale-up iterations. Data in red indicate less than favourable results; data in green, favourable results.

Table 1, at a pressure drop of 4 kPa and a flow rate of 40 L/min, in three replicate testing, the EM of powder from the device was very low, about 50% of the nominal dose, and the relative standard deviation was high, indicating a need for inventive re-engineering of the compartment design.

For that purpose, new inhaler designs were provided with additional lateral air vents in the shuttle, forming pairs at various heights of the powder compartment, each pair providing a non-tangential admission of air. The new constructions were then tested with the same payload of model drug particles and ultimately the EM of powder reached 91%, FPF was 41% of the emitted dose and both with high reproducibility. Powder retention within the compartment itself was observed to be residual.

This indicates that the re-design of TwinCaps[®] to achieve large dose delivery of challenging powders was experimentally successful and the new enhanced device was named TwinMaxTM.

Following the development process which used the model trehalose/leucine formulation, TwinMax was then tested with a spray-dried, API-only formulation



Figure 3: SEM image of spray-dried trehalose/leucine composite particles.

of a novel synthetic protein, AP301, intended for the treatment of pulmonary oedema arising from high altitude exposure, blood transfusions or lung infections.⁷ Targeting treatment in emergency situations through a single-use disposable inhaler, initial proof of concept results showed that TwinMax enabled a reproducible delivery of a total dose of 100 mg of a spray-dried drug-alone formulation, achieving a fine particle dose of 30 mg in *in vitro* aerodynamic performance characterisation studies.⁸

ENHANCED AERODYNAMICS

The result of the innovative re-engineering process of the powder compartment design presented in Table 1 is further detailed in Figure 4 through the use of computational fluid dynamics (CFD). The new compartment design is characterised by creating high flow velocity magnitudes at the bottom of the compartment and near the side walls, which induce non-uniform axial and tangential flow components varying across the powder compartment's length. These induce an air flow pattern with both high-flow turbulent kinetic energy and high flow vorticity within the compartment which effectively contribute to enhancing the primary powder dispersion mechanism for high dose drug delivery.

CONCLUSION

The interest in delivering high dose compounds to the lung, in the range of 100 mg or more of active ingredient, is driving the development of DPIs with enhanced dose delivery capability. Using



Figure 4: TwinMax CFD plot showing flow streamlines coloured by velocity magnitude. Compare with TwinCaps[®] in Figure 2. TwinMax displays faster velocities in the powder compartment due to additional side vents. Lower speeds in the mouthpiece are comparable in both devices.

fast development tools such as CFD and 3D printing, the currently marketed TwinCaps® DPI has been scaled-up to the new TwinMax design for high-dose delivery for single to short-term treatments and emergency situations. The TwinMax inhaler combined with spray-drying formulation technology has been shown to be capable of delivering a total dose of 100 mg of a drug and presents a simple, cost-effective solution to deliver drugs requiring large doses for effective therapy.

REFERENCES

- 1. Andrade G, Villax P, Vozone C, "The time has come". PMPS, 2015, February, pp30-33.
- 2. Khassawneh BY, Al-Ali MK, Alzoubi KH, Batarseh MZ, Al-Safi SA,

Sharara AM, Alnasr HM, "Handling of inhaler devices in actual pulmonary practice: Metered-dose inhaler versus dry powder inhalers". Respiratory Care, 2008, Vol 53(3), pp324-328.

- 3. Wieshammer S, Dreyhaupt J, "Dry powder inhalers: Factors associated with device misuse". Respiratory Drug Delivery Europe, 2009, Vol 1, pp95-104.
- Fisher B, Wong W, Fletcher DF, Traini D, Chan H, Young PM, "The use of computational approaches in inhaler development". Advanced Drug Delivery Reviews, 2012, Vol 64, pp312-322.
- Ruzycki CA, Javaheri E, Finlay WH, "The use of computational fluid dynamics in inhaler design". Expert Opin Drug Delivery, 2013,

Vol 10(3), pp307-323.

- Vehring R, "Pharmaceutical particle engineering via spray drying". Pharmaceutical Research, 2008, Vol 25(5), pp999-1022.
- Tzotzos S, Fisher H, Pietschmann H, Shabbir W, Lemmens-Gruber R, Lucas R, "AP301: development of inhalation medicine from scientific discovery to clinical proof-of-concept for life treatment of life-threatening pulmonary oedema". DDL25 proceedings, 2014, pp91-95.
- Lopes IS, Fisher B, Fisher H, Fernandes JV, Serôdio P, Neves F, "Combining Particle Engineering with Device Development to fine tune DPI performance of AP301". In Drug Delivery to the Lungs 26, 2015, The Aerosol Society, Bristol.

ABOUT THE AUTHORS

João Ventura Fernandes is Business Development Manager at Hovione Technology. A mechanical engineer with a PhD in Engineering Design and over eight years' experience in product design in the aerospace and pharmaceutical industries. He worked previously in product design at Volvo Aero and Rolls-Royce jet engines and joined Hovione in 2014, quickly becoming a skilled device developer, scientist and inventor.

Gonçalo Rebelo de Andrade is Director at Hovione Technology. He holds a Ph.D. in Biochemistry from Ludwig Maximillian University in Munich and earned his Lisbon MBA course degree at Nova/Catolica Business School. He joined the Hovione group in 2013 as a business development manager for inhalation drug development services and for the dry powder inhalers within Hovione's portfolio, which he led until March 2016. Gonçalo Andrade brings 15 years' experience in the life sciences sector in the US, Germany and Portugal where he worked for both large MNC companies and startups and a clear vision on the hurdles connected to the drug development of inhaled drugs.

Peter Villax is Chief Executive Officer at Hovione Technology. He joined Hovione in 1982 as a computer programmer, then switched to pharmaceutical development in 1990, soon becoming interested in pulmonary delivery and in the development of DPIs. In 2007 Hovione licensed TwinCaps® to Daiichi Sankyo for the delivery of Inavir®, becoming market leader in the influenza space in Japan. He acquired significant experience as an inventor of devices, as a patent writer and as licensor of technology patents.

SELECTION OF EXCIPIENTS FOR DRY POWDER INHALERS

As dry powder inhalers need a carrier to help with ensuring the drug is effectively delivered, interest has been focused on developing inhalation-grade lactose for this purpose. Harry Peters, Product Application Specialist Inhalation, and Gerald Hebbink, PhD, Scientist, both of DFE Pharma, look at which selection criteria to use to ensure the best grade of lactose is used for each dry powder inhalation formulation.

Dry powder inhalers (DPIs) have become very popular for dosing of medications to patients, especially those suffering from respiratory diseases. Most DPI formulations contain a carrier to improve the handling of the powder and to control the deposition of the drug into the lungs.^{1,2}

Excipients like lactose, mannitol, sorbitol, erythritol, anhydrous glucose, trehalose and fumaryl diketopiperazine (FDKP) have been investigated as carriers for use in DPI drugs.^{3,4} Some of these excipients are hygroscopic and are therefore not suitable for combination with every drug.³

Most formulations in the market use alpha-monohydrate lactose, which has been widely accepted by regulatory authorities.⁵ However, health authorities do require extra testing and controls for some parameters, compared with the use of lactose in oral dosage forms. Therefore, inhalation-grade lactose has been developed and is the preferred excipient for the use in DPI formulations.

During the R&D process for a DPI project, it should be understood what kind of functionality needs to be addressed with the lactose. Also in view of quality by design (QbD) regulations,^{6,7} the critical attributes of a DPI formulation that determine the functionality should be understood. A number of attributes of excipients have been identified.⁸ In this article several selection criteria are described that will determine which grade of lactose is optimal for any specific DPI formulation.

DRUG PROCESSING

Most inhaled formulations contain a highly potent pharmaceutical active that has been micronised and is dosed in low concentrations. Handling of micronised actives is a challenge due to agglomeration. To improve the handling, a carrier is added to de-agglomerate the active during blending. Almost all inhalation-grade lactose would give this functionality. The criterion to be evolved is that the surface area of the lactose is sufficient to de-agglomerate the active particles that stick to the lactose surface.⁹ Furthermore, the amount of powder that can be inhaled should be considered.

"One of the challenges for the formulator is to fill a device with the drug and obtain content dose uniformity."

DEVICES

Dry powder inhalation devices on the market can roughly be divided into three groups: capsule devices, blister devices and reservoir devices. The first step in a development process of a DPI is the selection of a device. Subsequently, the most important parameters for the selection of the optimal lactose grade are the filling platform, dosing of the drug out of the device and deposition of the drug in the lungs.

Once the device has been selected it has become clearer what the filling platform of the formulation could look like and what type of lactose is needed to fill and empty the device.¹⁰

One of the challenges for the formulator is to fill a device with the drug and obtain content dose uniformity. Filling systems nowadays can consistently fill small volumes of approximately 5 mg on commercial production scale. Since dosages of some actives are below 1 mg, the formulator will have to increase the mass of the powder with a carrier to ensure proper filling. Formulations containing more than 95% lactose are therefore quite common.



Harry J W Peters Product Application Specialist Inhalation T: +31 545 256703 E: Harry.Peters@dfepharma.com



Dr Gerald A Hebbink Scientist T: +31 545 256611 E: Gerald.Hebbink@dfepharma.com

DFE Pharma Kleverstrasse 187 47574 Goch Germany

www.dfepharma.com

Filling Reservoir Devices

Reservoir devices are often filled with a good flowing carrier, because the dosing of the formulation is metered by the device. The metering system requires sufficient flow and constant density of the powder to achieve good content dose uniformity. Good flowing lactose grades with constant density are recommended to be used in these types of devices. The mean particle size will mostly be in the range of 100–200 µm. Good flowing lactose grades are obtained mainly by sieving processes.

Filling Blister Devices

Blisters can be filled with different techniques. All techniques require that the powder stays in the pocket of the aluminium-seal of the blister before it is sealed. Therefore, the powder properties of the formulation should be non-dusting and slightly cohesive. Cohesiveness of the lactose can be increased by milling the lactose or by addition of fine lactose grades to the formulation.

Filling Capsule Devices

The type of lactose chosen here is dependent on the filling system. Capsule filling devices, like drum fillers and piston fillers, will require more cohesive, milled-grade lactose grades.¹¹ Tamper filling or other volume filling techniques like the "pepper shaker", however, require a free-flowing powder.¹² Sieved lactose grades will in general meet these criteria.

DRUG DEPOSITION

Literature describes that for specific devices the amounts of fine lactose particles plays a significant role in the deposition of the drug.^{13,14} Especially for the generic formulator, it is a challenge to meet the requested deposition with the same dose of drug, particularly when using a different device. The parameters that a formulator can use to optimise the deposition are restrained by the design of the device and expanded by the various lactose grades.¹⁵

DESIGN OF EXCIPIENT

From these selection criteria for excipients, it becomes clear that the excipients need to be designed specifically. There are several ways to do this, such as chemical and mechanical surface modifications.^{16,17} However, the most



Figure 1: Unit operations and combinations thereof for the design of lactose particle size distribution.

common technique of manipulating particle size distributions of lactose is through milling and sieving operations. By combining several of these techniques, as illustrated in Figure 1, a plethora of lactose grades can be designed.

CONCLUSION

The selection of the optimal inhalation lactose grade is based on the device, the filling platform, the concentration of the active, processing of the active and the required deposition of the drug in the lungs. Each formulation will therefore need the excipient to be designed to meet the specific requirements mentioned above. Although this selection is often empirical, support of an experienced excipient supplier can speed up the development process.

REFERENCES

- Pilcer G, Amighi K, "Formulation strategy and use of excipients in pulmonary drug delivery". Int J Pharm, 2010, Vol 392, pp1–19.
- Weers JG, Miller DP, "Formulation design of dry powders for inhalation". J Pharm Sci, 2015, Vol 104, pp3259–3288.
- 3. Steckel H, Bolzen N, "Alternative

sugars as potential carriers for dry powder inhalations". Int J Pharm, 2004, Vol 270, pp297–306.

- Rahimpour Y, Kouhsoltani M, Hamishehkar H, "Alternative carriers in dry powder inhaler formulations". Drug Discov Today, 2014, Vol 19, pp618–626.
- 5. Edge S, Kaerger JS, Shur, J, in Handbook of Pharmaceutical Excipients 6th ed (eds. Rowe RC, Sheskey PJ & Owen SC) pp362–364, Pharmaceutical Press, 2009.
- Yu LX, "Pharmaceutical quality by design: product and process development, understanding, and control". Pharm Res, 2008, Vol 25, pp781–791.
- Yu LX et al, "Understanding pharmaceutical quality by design". AAPS J, 2014, Vol 16, pp771–783.
- Kinnunen H, Hebbink G, Peters H, Shur J, Price R, "Defining the critical material attributes of lactose monohydrate in carrier based dry powder inhaler formulations using artificial neural networks". AAPS PharmSciTech, 2014, Vol 15, pp1009–1020.
- 9. Ferrari F et al, "The surface roughness of lactose particles can be modulated by wet-smoothing using a high-shear mixer".

AAPS PharmSciTech, 2004, Vol 5, e60.

- Grasmeijer F, Grasmeijer N, Hagedoorn P, Frijlink HW & Boer AH de, "Recent advances in the fundamental understanding of adhesive mixtures for inhalation". Curr Pharm Des, 2015, Vol 21, pp5900–5914.
- Sim S et al, "An insight into powder entrainment and drug delivery mechanisms from a modified Rotahaler[®]". Int J Pharm, 2014, Vol 477, pp351–60.
- 12. Edwards D, "Applications of capsule dosing techniques for use in dry powder inhalers". Ther Deliv, 2010, Vol 1, pp195–201.
- 13. Kinnunen H et al, "Extrinsic lactose fines improve dry powder inhaler formulation performance of a cohesive batch of budesonide via agglomerate formation and consequential co-deposition". Int J Pharm, 2014, Vol 478, pp53–59.
- Kinnunen H, Hebbink G, Peters H, Shur J, Price R, "An investigation into the effect of fine lactose particles on the fluidization behaviour and aerosolization performance of carrier-based dry powder inhaler formulations". AAPS PharmSciTech, 2014, Vol 15, pp898–909.
- 15. Grasmeijer F et al, "New mechanisms to explain the effects of added lactose fines on the dispersion performance of adhesive mixtures for inhalation". PLoS One, 2014, Vol 9, e87825.
- Singh DJ et al, "Preparation and evaluation of surface modified lactose particles for improved performance of fluticasone propionate dry powder inhaler". J Aerosol Med Pulm Drug Deliv, 2015, Vol 28, pp254-267.
- Williams D, "Particle Engineering in Pharmaceutical Solids Processing: Surface Energy Considerations". Curr Pharm Des, 2015, Vol 21, pp2677–2694.

ABOUT THE AUTHORS

Harry Peters is a technical support specialist in the use of lactose in pharmaceutical applications for more than 10 years. In the last six years at DFE Pharma he has further specialised in the dry powder inhalation field. He started working as R&D manager and product application specialist for inhalation grade lactose. He advices formulators of dry powder inhalers about the use of inhalation grade lactose. Together with customers, special lactose grades are developed to optimise the filling and performance of the devices and formulations. Together with iniversities and industry, new characterisation techniques are explored to further understand lactose in dry power formulations.

Gerald Hebbink is a chemist who has been working with lactose for the pharmaceutical industry for over eight years. He has been specialising in lactose for inhalation within DFE Pharma in close collaboration with industry partners and with universities all over the world. This has resulted in co-authorship of peer-reviewed papers on lactose, from production to application.



*Digital subscription is FREE. Print costs £189/vr (10 issues)



6-7 April 2017, London

Book before 10 February 2017 and SAVE £200/€280

Key topics to be covered:

- Nasal drugs to treat nasal disorders: a comprehensive review
- Formulation, deposition and effect of nasal medications
- Nose to brain drug delivery of Oxytocin
- Topical delivery in Chronic Rhinosinusitis with Polyps
- Benefit brought from latest dry powders vs liquid formulation
- Applying FDA combination drug product guidance to nasal spray products
- What are Chemisimilars and what's the problem?
- Case Study: Opioid overdose Developments in Intranasal Naloxone





OPTIMISING ANALYTICAL STRATEGIES FOR THE DEMONSTRATION OF BIOEQUIVALENCE IN A GENERIC NEBULISER

US FDA guidance for the *in vitro* demonstration of bioequivalence in a generic nebuliser directly references specific analytical strategies for the characterisation of aerosolisation performance. In this article, Déborah Le Pennec, Research Technician, University of Tours; Laurent Vecellio, R&D Engineer, University of Tours and Scientific Director, Aerodrug, DTF Medical; Paul Kippax, Team Leader, Advanced Materials, Malvern Instruments, and Stephane Rouquette, European Business Manager, Biosciences, also of Malvern Instruments, look at the optimal application of laser diffraction and automated imaging within this context.

The continuous drug delivery profile and ease of use of nebulisers makes them a popular choice for drug delivery, especially for high drug dosages and for paediatric or geriatric patients. Successful drug delivery relies on aerosolising a formulation to a particle size suitable for inhalation. Consequently, particle size measurements have an important role to play in supporting the *in vitro* demonstration of bioequivalence (BE) for a generic submission.

Draft product-specific US FDA guidance for nebulised Budesonide¹ highlights laser diffraction particle size measurement as one of the techniques that can be used to demonstrate BE in a nebuliser via *in vitro* testing alone – a valuable approach that minimises the need for more expensive studies. It also points to the need for agglomerate detection and measurement in suspension (in the ampoule) since this too can influence the effectiveness of drug delivery. In this article we examine the information provided by laser diffraction, within this context, and the optimisation of a test set-up for measurement,

"Laser diffraction particle size analysis allows the real-time measurement of droplet size in a nebuliser aerosol, making it complementary to the more time-consuming, but component-specific sizing delivered by cascade impaction. Furthermore, laser diffraction measurements can be made at varying flow rates, enabling direct assessment of the impact of inhalation and exhalation on inhaled droplet size."

Déborah Le Pennec Research Technician University of Tours, France

Laurent Vecellio Scientific Director Aerodrug, DTF Medical, France

Paul Kippax Team Leader, Advanced Materials Malvern Instruments

Stephane Rouquette

European Business Manager, Biosciences Malvern Instruments

Malvern Instruments Ltd

Enigma Business Park Grovewood Road Malvern WR14 1XZ United Kingdom T: +44 1684 892 456 F: +44 1684 892 789

www.malvern.com

presenting data showing the impact of a range of experimental parameters. We also investigate the complementary use of automated imaging as an efficient technique for the detection of agglomerates within formulation suspensions.

DEFINING THE PERFORMANCE OF NEBULISERS

Rather than delivering a pre-metered dose, nebulisers are loaded with a reservoir of drug formulation and operate continuously once activated. The liquid drug formulation is aerosolised using a jet, ultrasonic or mesh nebuliser, through the application of compressed air, ultrasonics or vibration, respectively, to form a fine mist which is inhaled by the patient. When using a nebuliser, the patient breathes normally so the aerosol cloud is drawn into the lungs under regular tidal breathing conditions. Rapid and efficient delivery of the drug to the target area of the respiratory tract is dependent upon aerosolising the dose to a fine particle size, typically below 5 µm, with optimum particle deposition in the alveoli associated with even finer particle sizes. The fraction of a dose that will deposit in the lungs on the basis of size is called the respirable fraction or the fine particle fraction (FPF).

Within the clinical setting, nebulisers can be loaded with a range of alternative formulations for However, comparison. the effectiveness of drug delivery depends directly on interactions between the formulation and the nebuliser device, so testing the two together has become standard practice. Key performance metrics are: delivered droplet size, because of its influence on pulmonary deposition; and the rate of drug delivery.

Figure 1: The test set-up for measuring particle size data for a nebuliser with Spraytec laser diffraction system, showing the variables that can be optimised.

DEMONSTRATING BIOEQUIVALENCE IN NEBULISERS

In the development of generics, the aim is to duplicate the performance of an established product precisely so that both innovator and generic can be used interchangeably to deliver an identical therapeutic effect. Identifying *in vitro* analytical strategies and instrumentation that provide the required information to demonstrate BE helps developers avoid the costs and time associated with *in vivo* testing and extensive clinical trials.

Steadily rising numbers of generic submissions have increased the regulatory burden of assessing and addressing concerns over the suitability of an *in vitro* testing strategy for any given product.

In response, the FDA has released a number of product-specific draft guidances detailing the tests required for popular targets. Nebulised budesonide, a steroid widely used for the treatment of asthma and chronic obstructive pulmonary disease (COPD), is one of the inhaled products for which product-specific draft guidance is already in place.¹

This draft guidance for budesonide highlights seven discrete tests for the demonstration of bioequivalence by *in vitro* testing alone, including: "Comparative

Transmitter

aqueous droplet size distribution of the nebulised aerosol by a laser diffraction method," and the need for "comparative drug particle and agglomerate particle size distribution in the suspension (in the ampoule)".

The following experimental studies show how laser diffraction and automated imaging can be optimally applied to meet these requirements.

STUDY 1: OPTIMISING LASER DIFFRACTION MEASUREMENTS

Laser diffraction particle size analysis allows the real-time measurement of droplet size in a nebuliser aerosol, making it complementary to the more time-consuming, but component-specific, sizing delivered by cascade impaction. Furthermore, laser diffraction measurements can be made at varying flow rates, enabling direct assessment of the impact of inhalation and exhalation on inhaled droplet size.

Researchers at the University of Tours (CEPR, INSERM U1100, Tours, France) use laser diffraction particle size analysis routinely to study the performance of standard jet, breath-enhanced jet and mesh nebulisers. To support this work, a series of experiments were carried out to optimise the analytical method used, by investigating the impact of certain

Hose to filter and vacuum pump

Nebulizer

Receiver

experimental parameters on the measured data. All tests were carried out using a Spraytec laser diffraction analyser for particle size measurement (Malvern Instruments, UK) and a PARI LC PLUS nebuliser with a Pariboy compressor (PARI, Germany) as recommended in the FDA guideline for budesonide.¹ Aspiration of the sample was carried out at flow rates in the range 0 L/min to 100 L/min using a vacuum pump (Copley Scientific, UK). All measurements were made using 2 mL of saline solution over the course of 1 min.

Figure 1 shows the experimental set-up used and the method parameters that were varied, which included:

- X distance: the distance from the spray plume centre to the receiver lens along a central line between the detector and transmitter, across the range 1-32 cm
- Y distance: the distance of the nebuliser from the laser beam passing through the laser diffraction measurement zone, across the range 1-7 cm
- Z distance: the distance between the laser and the extraction system used to collect the aerosol created by the nebuliser, across the range 5-11 cm
- Extraction flow rate, across the range 0 L/min to 100 L/min.

"An optimised method was developed ... This provides valuable support for the use of laser diffraction to assess the performance of jet nebulisers robustly, either in BE studies or more generally."

The impact of these variables was quantified by recording:

- Dv10, Dv50 and Dv90: the measured diameters below which 10%, 50% and 90% of the particle population lies, on the basis of volume
- Span: defines the width of the particle size distribution and is equal to (Dv90 - Dv10)/Dv50
- % of the sample below 5 µm in size, which quantifies the sensitivity of the measured FPF.



Figure 2: Maximum variability data for particle size distribution metrics measured using different laser diffraction / nebuliser set-ups. X distance (between the nebuliser spray plume and the receiver) is highlighted as a key parameter.



Figure 3: Dv10, Dv50, Dv90 and the % particles <5 μ m, as a function of the distance between the nebuliser and the receiver lens. These data confirm that the measurement is robust to changes in distance in the 1-14 cm range.



Figure 4: Dv10, Dv50, Dv90 and the % particles <5 μ m, as a function of the distance between the nebuliser and the laser beam. These data show that moving the device too far away from the laser compromises sampling of the aerosol.

Figure 2 summarises the maximum variability associated with each parameter, calculated by considering the difference in the values obtained for the minimum and the maximum control value (e.g. 1 cm and 32 cm for the X distance). Generally speaking, measurements are robust with respect to the experimental set-up, especially the reported figures for the percentage of material below 5 µm. However, it is clear that the X distance, which describes the position of the nebuliser relative to the receiver lens, has the largest impact on the variability of the reported results. Y distance, the distance between the nebuliser and the laser, is the second most influential parameter.

The change in the reported size distribution parameters as the X distance is altered relates directly to the way the laser diffraction technique operates. Laser diffraction systems calculate droplet size distributions by measuring the light scattered from the spray droplets as they pass through the laser beam. As the nebuliser spray plume is moved further away from the receiver optics, there is a point at which light scattered at wide angles is no longer collected effectively (an effect called vignetting). This affects the ability of the system to detect smaller particles, causing changes in the reported values for the Dv10 and percentage of particles below 5 µm. In addition, there is an impact on the ability of the system to measure the width of the distribution, causing a variation in the reported Dv90 and Span. The influence of vignetting increases as the distance increases, as clearly shown in Figure 3 which confirms that the results obtained are robust in the range 1-14 cm but then change rapidly at larger distances. However, the fact that the nebuliser can be positioned up to 14 cm away from the receiver without a significant impact on the result is advantageous as it minimises the risk of spray deposition on the receiver optics.

An additional consideration is the sampling of the aerosol. Laser diffraction will only measure particles which pass through the measurement laser beam. Changing the Y distance leads to a change in the width of the spray plume at the point where it crosses the laser, which will in turn cause a change in the measurable percentage of the plume. Y must therefore be controlled to ensure that all droplets are sampled. The results gathered show that increasing Y distance causes the Dv90 to increase and the % particles <5 µm to decrease (Figure 4), suggesting that sampling of the spray



Figure 5: Dv10, Dv50, Dv90 and the % particles <5 μ m, as a function of the distance between the laser beam and the extractor. This data shows that moving the extractor further away from the measurement zone results in a slight reduction in measured particle size.

Parameter	Setting	Comments	
X-distance	1-6 cm	Ensure that optical contamination is minimised whilst also avoiding vignetting	
Y-distance	1 cm	Measures close to the laser to ensure good sampling of the entire spray plume	
Z-distance	5 cm	Ensures good extraction with minimal impact to the plume width	
Extration Flow Rate	Use the lowest possible flow rate to avoid backflow or recirculation of the aerosol within the laser beam		

Table 1: Optimised method parameters for nebuliser characterisation by laser diffraction.

"Speed of measurement, measurement reproducibility, and the number of particles that can be characterised in a single experiment make automated imaging a practical alternative to manual microscopy."

plume is impacted by moving the device too far from the beam.

A possible rationale for the observed results is that the fines are recirculating before they reach the laser beam, causing them to be lost prior to measurement.

In this study, the impact of the distance between the extractor and measurement zone, Z distance, which is controlled to ensure that all droplets pass through the

measurement zone without recirculation, was found to be minimal (see Figure 5). However, a slight decrease in particle size is observed at larger Z distances, with recirculation the most probable cause. Similarly, the extraction flow rate, which also influences recirculation, was also observed to have a minimal effect with this set-up (data not shown).

An optimised method was developed for subsequent studies, taking all of the measured data into account (see Table 1). This provides valuable support for the use of laser diffraction to assess the performance of jet nebulisers robustly, either in BE studies or more generally.

STUDY 2: AUTOMATED IMAGING TO COMPARE AGGLOMERATION

Automated imaging systems capture images of individual particles in a sample to build up statistically significant distributions of particle size and shape. Speed of measurement, measurement reproducibility,



Figure 6: Particle size distribution data for the reference budesonide formulation indicates that there are agglomerates present which are dispersed by the application of ultrasound.



Figure 7: Particle size distribution data for the test budesonide formulation indicates that particle size is relatively unaffected by the application of ultrasound.

and the number of particles that can be characterised in a single experiment make automated imaging a practical alternative to manual microscopy. By combining particle size and particle shape data, automated imaging makes it easy to investigate and classify specific particle populations within a sample. For example, shape data can often be used successfully to differentiate agglomerates from primary particles. These capabilities make automated imaging a useful tool for nebuliser formulation development, and the demonstration of BE in accordance with FDA guidance.

In an experimental study, the particle size and state of agglomeration was studied in samples of innovator (reference) and generic (test) budesonide nebuliser formulations, before and after the application of ultrasound. Measurements were made after 0, 1, 2 and 3 minutes of ultrasound. For each measurement, 3 µL of sample was pipetted on to a glass microscope slide. A glass cover was placed over the sample and sealed in place, and the sample was then subjected to automated imaging using a Morphologi G3 automated imaging system (Malvern Instruments, UK). This measurement procedure was repeated four times for each sample, with the resulting data combined to form a single record for each sample. Particle size distribution data were presented in terms of circle equivalent (CE) diameter – the diameter of a circle with the same area as that of the particle.

The application of ultrasound reduced the overall particle size of the reference formulation (see Figure 6). Images of the largest particles in the sample clearly show agglomerated material in the original formulation that were not present in the samples after they were subjected to ultrasound. The particle size of the test formulation was, in contrast, relatively unchanged by the application of ultrasound and there was no evidence of agglomerates (see Figure 7).

In comparing these two formulations it is clear that they have somewhat different properties. The innovator is less stable than the generic, forming loose agglomerates which are relatively easily dispersed. However, the dispersed or primary particle size in both formulations is closely similar. Cascade impaction could be usefully applied as a follow-up analysis to determine whether any agglomerates present are dispersed during nebulisation, to support a claim of bioequivalence.

CONCLUSION

Draft product-specific guidance for the nebulised delivery of budesonide highlights laser diffraction particle sizing for the *in vitro* demonstration of bioequivalence. The data presented here illustrate the insight that laser diffraction measurements can provide in nebuliser studies and demonstrate how to optimise a test method for its beneficial application within this context.

Automated imaging is highly complementary to laser diffraction and efficiently enables particle size and agglomerate measurement in the formulation, as recommended in the regulatory guidance. The results presented here show how automated imaging can be used to detect agglomerated particles and assess the ease with which they are dispersed to support the demonstration of BE.

REFERENCE

1. Draft US FDA Guidance for Budesonide (Suspension/Inhalation). Recommended Sep 2012. (http:// www.fda.gov/downloads/Drugs/.../ Guidances/UCM319977.pdf)

FROM SPRAYS...

SPRAYTEC

Rapid particle and droplet size analysis

- Measures spray concentration and particle / droplet size during device actuation
- Aids rapid screening and accelerated development of OINDP formulations and devices
- Promotes a knowledge-based approach to product development advocated by QbD.

www.malvern.com/spraytec

CHARACTERIZE YOUR OINDP IN **DETAIL**



...TO API SIZE

MORPHOLOGI G3-ID

Morphologically Directed Raman Spectroscopy

- Component specific particle size and shape distribution measurements for OINDP formulations
- Provides supporting evidence for in-vitro bioequivalence and CMC studies for nasal sprays
- Aids the deformulation of OINDP formulations, promoting a QbD focused approach to ANDA submissions

www.malvern.com/g3id



www.malvern.com



BAUMANN MEDICAL

SPRINGS AND STAMPINGS FOR MEDICAL DEVICES

www.baumann-group.com

For more than 125 years, BAUMANN Group has been a symbol of Swiss precision and quality. We are known worldwide as a leading company in spring and stamping manufacturing. The family-owned group, now in its fifth generation, employs more than 1,500 people at eleven production sites around the globe. Its dedicated medical divison with medical mindset complies with ISO 13485 and addresses the specific customer needs of the medical and pharmaceutical industries in the fields of drug delivery, syringes, blood collection, diagnostics, and airway products.

For further interest and information contact BAUMANN MEDCIAL: medical@baumann-group.com