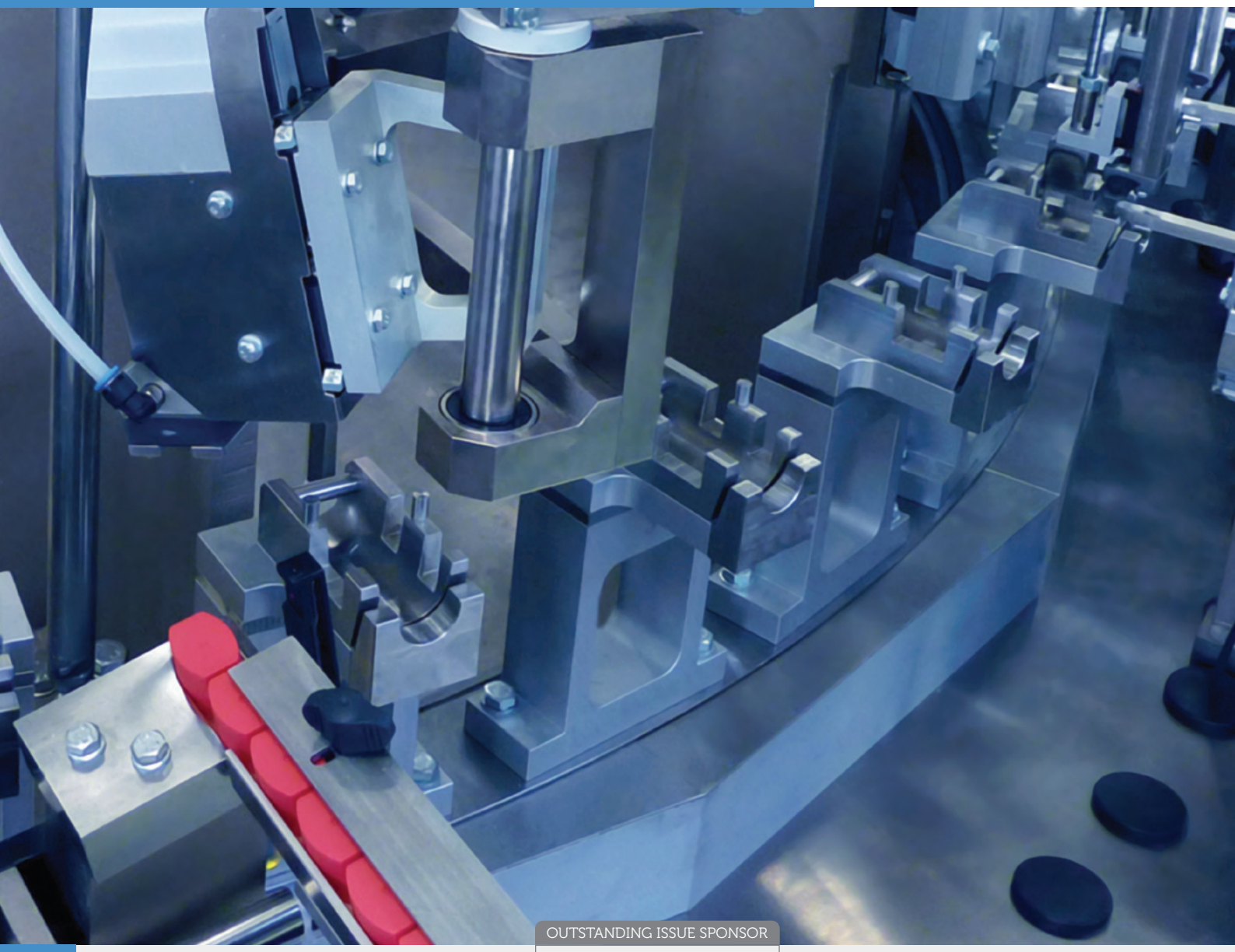
PULMONARY & NASAL DELIVERY

ON drugDELIVERY



OUTSTANDING ISSUE SPONSOR

3M

AERO drug

CAPSUGEL®

Catalent

Hovione

Nemera

SCS SPECIALTY COATING SYSTEMS™

DECEMBER 16TH, 2014 • ISSUE NO 53

ONdrugDelivery Issue Nº 53, December 16th, 2014

Pulmonary & Nasal Delivery

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

EDITORIAL CALENDAR 2015

Jan Ophthalmic Drug Delivery
Feb Prefilled Syringes
Mar Transdermal Patches, Microneedles & Needle-Free Injection
Apr Pulmonary & Nasal Drug Delivery
May Injectable Drug Delivery: Devices Focus
Jun Novel Oral Delivery Systems
Jul Wearable Bolus Injectors
Oct Prefilled Syringes
Nov Pulmonary & Nasal Drug Delivery
Dec Delivering Biotherapeutics

SUBSCRIPTIONS:

To arrange your **FREE** subscription (pdf or print) to ONdrugDelivery Magazine:
E: subscriptions@ondrugdelivery.com

SPONSORSHIP/ADVERTISING:

Contact: Guy Furness, Proprietor & Publisher
T: +44 (0) 1273 47 28 28
E: guy.furness@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 Furness 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

Front cover image: "Mouthpiece cover fitting process integrated in RTS Platform", provided by teamtechnik Group. Reproduced with kind permission.

CONTENTS

Offering the Shortest Path to Market with our Unique Inhalation Technology Platform

Providing a uniform dose in a portable, easy-to-use system, capsule-based DPI is a simple and cost-effective way to deliver medication via the pulmonary route. Capsugel's capsules are custom engineered to provide optimal performance between the capsule/device and capsule/formulation to achieve the highest safety and efficacy of the drug product. Complementing Capsugel's 20 years expertise in specialized inhalation capsules, Bend Research provides a full range of services and know-how in particle engineering for small and large molecules, as well as fast track programs for new chemical entities and generics.

Contact us today to learn more about our unique technology platform for inhalation drug delivery.

dpicapsule.com +33 3 89 20 57 25

CAPSUGEL®

EXPERT REVIEW
THE SIGNIFICANCE OF INHALER TECHNIQUE & HOW TO IMPROVE IT

In this review piece, Professor David Price, Professor of Primary Care Respiratory Medicine, University of Aberdeen, describes a significant and long-standing unmet need for inhaler technique to be improved in patients with asthma and COPD, and sets forth strategies to achieve the sorely needed improvements.

INTRODUCTION

Respiratory care has evolved enormously over the last 50 years, but most of the issues faced by patients in terms of competent inhaler use have not changed at all. A number of critical drivers have had an impact on the growth of the respiratory care area, including: changes in treatment approach with a focus on health promotion rather than illness treatment and an emphasis on outpatient treatment rather than hospital admission; the increase in aging population with chronic respiratory disease; advancements in technology and patient demand for simple and user friendly devices; and health service economic constraints

Current treatment approaches for asthma and COPD comprise combination therapy with an inhaled corticosteroid (ICS) and long-acting beta agonist (LABA), which can be an effective solution for the control of symptoms and prevention of exacerbations for many patients.[1]

Whilst it is known that correct use of inhalation devices is essential to ensure effective treatment. Many asthma and chronic obstructive pulmonary disease (COPD) patients remain undertreated as a consequence of poor inhaler technique.[1] Poor technique can impact drug delivery to the lungs leading to inadequate therapeutic benefit and increased risk for future asthma exacerbations. This in turn can lead to non-adherence [2] which has a significant impact on disease control in the asthma patient population and leads to increased economic burden.

At the recent Annual Meeting of European Respiratory Society (ERS), which took place in Munich, Germany on September 6-10, 2014, the symposium "Inhaler technique: human error or design challenge?", sponsored by Teva Pharmaceuticals, ignited debate on key issues such as under-treatment of asthma and COPD, the limitations of current inhaled therapies, and where the responsibility for good technique lies. Apart from the author, another discussant at the symposium was Professor Helen Reddel of the Woolcock Institute of Medical Research (Sydney, Australia). Her four-step plan to improving asthma control led to a shift in focus on inhaler technique in the most recent Global Initiative for Asthma (GINA) guidelines.

ASSUME INHALER TECHNIQUE IS INCORRECT UNTIL PROVEN OTHERWISE

Numerous studies have found that despite many efficacious medicines, asthma control continues to be a problem for at least half the patient population, leading to frequent need of rescue medication, increased risk of exacerbations and limited activity.[3,4]

- Poor asthma control leads to increased demand for urgent medical attention [5,6,7]
- In both asthma and COPD, one or more critical errors in inhaler technique were associated with a 50% increase in the need for a corticosteroid course, hospital admission or emergency visit [8]
- Systematic assessments [9] have found that 39% of patients have poor technique, 50% of them had poor technique and poor adherence
- Factors associated with poor technique include age, limited education, lack of training and prescription of multiple devices [10]
- Inhaler devices are complex and their use requires multiple steps
- Few HCPs can demonstrate correct use of inhalers [11,12,13]

Before GINA 2014,[14] many guidelines had given what may be perceived as an easier solution to poorly controlled asthma, there was a dependency on stepping up medication as a first step to control the condition.

A four-step plan to improve asthma control:

1. It may seem obvious but choose the most suitable device for the individual patient – it always helps as a healthcare professional to be able to use it yourself correctly without any instruction

Professor David Price
Professor of Primary Care Respiratory Medicine
E: david@rirl.org
T: +44 1223 967 855
M: +44 7787 905 057

Academic Primary Care
Division of Applied Health Sciences
University of Aberdeen
Polwarth Building
Aberdeen
AB25 2ZD
United Kingdom

Research in Real Life (RiRL)
16 Raffles Quay
#33-03 Hong Leong Building
Singapore 048581

www.rirl.org

Inhaler	Critical Error
Metered dose inhalers (MDIs) without a spacer	Failure to remove cap
	Not holding inhaler upright
	Actuation not corresponding to inhalation; actuation before inhalation
	Actuation not corresponding to inhalation; actuation is too late (Puff 1)
	Failure to actuate
	Failure to inhale
	Inhale too fast
	Inhalation through the nose
	When asked, patient does not know how to tell that their device is empty
Metered dose inhalers (MDIs) with a spacer	Failure to ensure a tight seal when mouthpiece is inserted into spacer. There
	should be a click heard with the Volumatic and with the AeroChamber device.
	It should be inserted with tight seal and the inhaler should be vertical at 90
	Failure to hold spacer with inhaler upright
	Failure to actuate just one dose into the spacer (either no dose actuated or actuates more than one dose)
	Spacer mouthpiece is inserted correctly but failure to seal lips
	Failure to inhale through mouthpiece within two seconds of discharging one dose
	Failure to actuate a dose into the spacer
	Failure to inhale
	Inhalation through the nose
	Failure to hold breath (or to hold for <3 s)
	When using two doses, starting to inhale through mouthpiece within two seconds of discharging the first dose
	Coughing during the inhalation
	If prescribed Fostair (beclometasone + formoterol), failure to know that they should use their inhaler within 20 weeks/five months after receiving it from the pharmacy
	Spacer has faulty parts, valves, or cracks in the plastic
	Having washed the device in soapy/detergent water
	Failure to air dry the device
	Failure to remove the cap
Dry powdered inhalers (DPI): Diskus	Failure to slide cover as far as possible
	Failure to slide lever fully to open mouthpiece
	Holding in a downward position after dose preparation (before inhalation)
	Shaking after dose preparation
	Blowing into the device before inhalation
	Failure to put in mouth and seal lips around mouthpiece
	Inhalation is not forceful from the start
	Failure to inhale through mouthpiece
	Inhalation through the nose
	Failure of the patient to know when the device is empty
Dry powdered inhalers (DPI): Turbohaler	Failure to remove cap
	Shaking during preparation
	Device not held upright (mouthpiece skywards) when the base is twisted during dose preparation (within 45)
	Dose not prepared correctly twisting the base until it clicks
	Dose not prepared correctly turning it back to the original position
	Shaking after dose preparation
	Failure to put in mouth and seal lips around mouthpiece
	Inhalation is not as fast as the patient can achieve (defined as a very fast suck)
	Inhalation is not forceful from the start
	Failure to inhale through mouthpiece
	Inhalation through the nose
	Failure to breathe out slowly to empty the lungs
	Breathing out into the device before inhalation
	Failure to tilt head such that the chin is slightly upwards
	Inhalation is not as long as the patient can achieve
	Failure to hold breath (or to hold for less than three seconds)
	Failure to replace cap after second inhalation

Table 1: Summary of usage, handling and technique errors associated with four different inhalers / inhaler types.

2. Check technique at every opportunity – everyone in asthma care is responsible!
3. Use an effective mode of training – physical demonstration better than written instruction
4. Inhaler skills training must be repeated – for both patients and healthcare professionals.

Inhaler technique is an integral part of the GINA 2014 asthma management strategy. Instead of the usual step-up of medication when control is poor, checking of inhaler technique and adherence should take place first.[14]

It's critical we understand how inhalers work in real life since the patients we often see in consultations are not typically the ones who participate in clinical studies. As we see more inhaler errors, we also see more asthma instability[5] – clearly this is an important association.

Several limitations of clinical research are important to note. There are systematic reviews that have even made their way into British asthma guidelines which say there are no differences between different inhaler devices! – this a result of all studies used being licensing studies for different devices. The entry criteria pose a challenge as, ethically, a study participant cannot be randomised to a device they cannot use, so patients are only randomised if they could manage the device(s) included in the trial, which obviously leads to equal outcomes.

THE DEVICE MATTERS

Regulatory clinical trials (RCTs) tend to focus on the drug, not the device. However, an old drug in a new improved inhaler might be better than a new drug in older, more complex inhalers. A device that is easy to teach and easy to maintain technique with can provide the best control over time.

WHAT SORT OF EVIDENCE DO WE NEED?

The Respiratory Effectiveness Group's review of existing evidence has demonstrated that current inclusion criteria for an average asthma trial are too restricted, e.g. lung function 50-80% predicted, 15% reversibility, perfect inhaler technique, non-smoker, no comorbidities, perfect adherence, still symptomatic, willing to fill in a diary twice a day, etc.[15]

Most patients do not have their technique checked as regularly in real life compared with in a trial, enough normal ongoing care needs to be observed to understand truly how an inhaler can make a difference. Registration RCTs should not be used as part of a meta-analysis if we want to evaluate the association between inhaler technique and inhaler device and outcomes – alternatives such as longer-term Phase III trials or more pragmatic RCTs could be considered. A more pragmatic RCT will allow for broader inclusion criteria and a type of care that better reflect normal, real life.

Even this solution is still not a truly representative sample so there is a real need for "real life" data to complement this, for example, observational studies. In 13 years of guidelines, there has been no change to inhaler technique!

In the real world, patients usually use their inhalers incorrectly:

- 61% of patients are still getting their pMDI technique wrong even after three attempts [16]
- 90% of patients are making errors [17]
- 55% of people made at least one serious error with GSK's Diskus, often presented as the device associated with the least errors.

Another important point is that we healthcare professionals are not great at assessing technique. Frequently the reason we get it wrong is that we don't know how to use the device ourselves.[18] Additionally, spacers are often provided as a lazy solution but still require education and training.

Presented at the ERS meeting, and published in Respiratory Medicine,[19] Table 1 summarises handling and technique errors associated with different types of inhaler – MDIs without a spacer, MDIs with a spacer, the Diskus DPI, and AstraZeneca's Turbohaler DPI.

ELIOT STUDY

Continuing the theme that data about real-life inhaler technique is both different from and more relevant than information collected in RCTs, the 2014 ELIOT (Easy Low Instruction Over Time) study, sponsored by Teva, set out to explore how well patients maintain their technique.

- ELIOT is a novel, pragmatic, prospective trial which compares steps to mastery, and maintenance of mastery, for Spiromax® *versus* Turbohaler®
- A 12 week randomised, open-label, parallel group study which only included patients who have never used either device before
- The study better represents the real-life scenario where patients go for many months between technique assessments
- This is an important and brave study as it's one of the few prospective randomised trials comparing different inhaler technique and different inhalers.

SUMMARY

Poor inhaler technique is widespread with the majority of patients making at least one critical error, and incorrect inhaler use is linked with uncontrolled asthma. Responsibility for ensuring correct technique lies with everyone in respiratory care. However, this also needs to be supported by innovation in inhaler design and technology. An optimal inhaler should be easy for a healthcare professional to teach and intuitive for a patient to use over an extended period of time. RCTs often focus on the drug inside, not the device itself which is just as important whereas real life and observational studies can provide a truer picture of how well inhalers really work and affect patient outcomes.

REFERENCES

1. *Molimard M, Raherison C, Lignot S et al, "Assessment of handling of inhaler devices in real life: an observational study in 3811 patients in primary". J Aerosol Med, 2003, Vol 16(3), pp 249-254.*
2. *McHorney C, "The Adherence Estimator: a brief, proximal screener for patient propensity to adhere to prescription medications for chronic disease". Curr Med Res Opin, 2009, Vol 25, pp 215-238.*
3. *Rabe K, Adachi M, Lai C, Soriano J, Vermeire P, Weiss K, Weiss S, "Worldwide severity and control of asthma in children and adults: the global asthma insights and reality surveys". J Allergy Clin Immunol, 2004, Vol 114(1), pp 40-47.*
4. *Murphy K, Meltzer E, Blaiss M, Nathan R, Stoloff S, Doherty D, "Asthma management and control in the United States: results of the 2009 Asthma Insight and Management survey". Allergy Asthma Proc, 2012, Vol 33(1), pp 54-64 (doi: 10.2500/aap.2011.32.3518. Epub 2011 Dec 15.)*
5. *Giraud V, Roche N, "Misuse of corticosteroid metered-dose inhaler is associated with decreased asthma stability". Eur Respir J, 2002, Vol 19(2), pp 246-251.*
6. *Lavorini F, Magnan A, Dubus J et al, "Effect of incorrect use of dry powder*

inhalers on management of patients with asthma and COPD". Resp Med, 2008, No 102, pp 593–604.

7. *Levy M, "Obtaining outcome data on asthma management: the UK National Review of Asthma Deaths". Prim Care Respir J, 2012, Vol 21(1), p 18. (doi: 10.4104/pcrj.2012.00017.)*
8. *Melani A, Bonavia M, Cilenti V, Cinti C, Lodi M, Martucci P, Serra M, Scichilone N, Sestini P, Aliani M, Neri M, "Gruppo Educazionale Associazione Italiana Pneumologi Ospedalieri. Inhaler mishandling remains common in real life and is associated with reduced disease control". Respir Med, 2011, Vol 105(6), pp 930-938. (doi: 10.1016/j.rmed.2011.01.005. Epub 2011 Mar 2. Erratum in: Respir Med. 2012 May;106(5):757.)*
9. *Crompton G, Barnes P, Broeders M, Corrigan C, Corbetta L, Dekhuijzen R, Dubus J, Magnan A, Massone F, Sanchis J, Viejo J, Voshaar T, "Aerosol Drug Management Improvement Team. The need to improve inhalation technique in Europe: a report from the Aerosol Drug Management Improvement Team". Respir Med, 2006, Vol 100(9), pp1479-1494. (Epub 2006 Feb 21. Review.)*
10. *Sestini P, Cappiello V, Aliani M, Martucci P, Sena A, Vaghi A, Canessa P, Neri M, Melani A, "Associazione Italiana Pneumologi Ospedalieri Educational Group. Prescription bias and factors associated with improper use of inhalers". J Aerosol Med, 2006, Vol 19(2), pp 127-136.*
11. *Guidry G, et al, "Incorrect use of metered dose inhalers by medical personnel". Chest 1992, Vol 101(1), pp 31-33.*
12. *Chopra N, et al, "Does introduction of new "easy to use" inhalation devices improve medical personnel's knowledge of their proper use?" Ann Allergy Asthma Immunol, 2002, Vol 88(4), pp 395-400.*
13. *Basheti A, et al. "User error with Diskus and Turbuhaler by asthma patients and pharmacists in Jordan and Australia". Respir Care, 2011, Vol 56(12), pp 1916-1923.*
14. *The Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA) 2014. Available from: http://www.ginasthma.org.*
15. *Roche N, Reddel H, Agusti A, Bateman E, Krishnan J, Martin R, Papi A, Postma D, Thomas M, Brusselle G, Israel E, Rand C, Chisholm A, Price D, "Respiratory Effectiveness Group. Integrating real-life studies in the global therapeutic research framework". Lancet Respir Med, 2013, Vol 1(10), pp 29-30. (doi: 10.1016/S2213-2600(13)70199-1. Epub 2013 Dec 2.)*
16. *Haughney J, et al, "Choosing inhaler devices for people with asthma: current knowledge and outstanding research needs". Respir Med, 2010, Vol 104, pp 1237-1245.*
17. *Price D, et al, "Assessment of potentially important device errors performed by asthma patients in the global iHARP review service". Abstract presented at IPCRG 2014*
18. *Molimard M, Raherison C, Lignot S, Depont F, Abouelfath A, Moore N, "Assessment of handling of inhaler devices in real life: an observational study in 3811 patients in primary care". J Aerosol Med, 2003, Vol 16(3), pp 249-254.*
19. *Price D, et al, "Inhaler competence in asthma: Common errors, barriers to use and recommended solutions". Resp Med, 2013, Vol 107(1), pp 37-46.*

EXPERTISE IN DEVELOPMENT, MANUFACTURING AND COMMERCIALISATION CONTRIBUTE TO SINGLE-CYCLE REVIEW FOR NOVEL MDI

In this case study, 3M Drug Delivery Systems reports on how its deep expertise in the development of MDIs enabled it to overcome a significant formulation challenge, achieve a single cycle FDA review, introduce a brand new dose-counter, and align and integrate manufacturing across two sites in different countries.

It takes significant expertise and outstanding management to launch a novel metered-dose inhaler (MDI) with a single-cycle US FDA review. 3M Drug Delivery Systems recently achieved this feat, not only formulating, scaling-up and commercialising a new product, but also introducing a patient-friendly dose-counter technology.

> "It takes significant expertise and outstanding management to launch a novel metered-dose inhaler (MDI) with a single-cycle FDA review. 3M DDS recently achieved this feat"

AN INNOVATIVE FORMULATION

The development process for the new combination MDI product began with a significant formulation challenge. One of the compounds in the product had previously been developed for use in a dry-powder inhaler, but never for an MDI. The surface energy of the compound is such that particles are attracted to each other and get larger over time. The resulting shift in particle size distribution makes this compound unstable at first glance. However, after experimentation, 3M's experts were able to devise a solution which involved the introduction of a 3M proprietary manufacturing process. Post-implementation testing showed that the product was very stable and consistent.

"This was a unique and innovative project," said Richard Beesley, New Business Development Manager at 3M Drug Delivery Systems. "When we develop products, we recognise that the stability of the active pharmaceutical ingredient is key. In this case, our understanding of the particle engineering – the science of the particles and micronisation of the drug – allowed us to make some predictions about particular formulations and pick a winning one. In this industry that is unique; nobody else does that."

ENSURING A SMOOTH TRANSITION TO COMMERCIALISATION

Once the project moved out of R&D into commercialisation, 3M's expertise again proved invaluable, with the team working to ensure a smooth transition into manufacturing at its Loughborough, UK plant. Several modifications were required at the manufac-

3M Drug Delivery Systems
3M Center, Building 275-03-E-10
St. Paul
MN 55144-1000
United States

T: 1 800 643 8086
E: dds@mmm.com

www.3M.com/InhalationExpertise

turing facility to accommodate the new product. First, because the product used a different propellant from many other MDIs, 3M worked with its engineering team to install a system to store this new propellant and pump it to the manufacturing lines. Additionally, the new manufacturing process required further concentrate manufacturing equipment and associated facilities to be installed.

ADDING VALUE WITH A DOSE COUNTER

Concurrently, 3M was also working to develop and manufacture a brand new dose counter to be incorporated into the inhaler. The 3M™ Integrated Dose by Dose Counter (see Figure 1) is designed to eliminate under-counting and over-counting, and has a familiar look and clear display so patients can use it with little or no training. This MDI product represented an ideal opportunity to introduce this specific dose counter to the market.

The dose counter was being manufactured in Germany, necessitating careful management from afar to align its production smoothly with the manufacturing in Loughborough.

"It can be quite difficult managing a supply chain that's at a distance from you, and it was also the first time 3M had used this dose counter technology," said Christine Hart, Project Manager for 3M Drug Delivery Systems. "However, managing global supply chains is a strength for 3M and something we have significant experience in, so we were able to call on that experience in the manufacturing of the dose counter, and ultimately, the final product."

A GLOBAL PLAN

Figure 1: MDI incorporating the 3M™ Integrated Dose Counter, manufactured by 3M Drug Delivery Systems.

Hart explained that the client's global launch plan demanded seamless co-ordination between countries, as the client planned to package the product at sites in both the US and in Ireland for its markets around the world.

"We worked with our client's supply chain to make sure those sites were lined up with shipping documentation, quality documentation, certificates of analysis, and more," she said. "You have to get it right, otherwise you may encounter interruptions at customs."

SINGLE-CYCLE SUCCESS

3M also readied its facility and processes for the FDA's pre-approval inspection (PAI) audit, and trained staff extensively to prepare for the handover from development to operations teams. With its long experience in the MDI market and its expertise in the regulatory process, 3M was able to achieve a single-cycle review for the new product, accelerating its speed to the market and optimising revenues for the client.

"Clients lose time when the FDA comes back with questions or says the package is inadequate for the review cycle," said Hart. "We leverage a very sound regulatory department with good expertise – we know what is required and anticipate needs in these reviews. When the FDA does an audit, they are on-site for a period of time and it's a very heavy review of all the documentation, the production line, batches made in the past and more. There was not an issue raised in our PAI audit; it was a green light from start to finish, so at the end, there were no snags and we achieved a single-cycle review."

In fact, 3M's expertise in MDIs is so in-depth that it is the only company that has been involved with every FDA MDI submission during the past five years – all of which have achieve a single-cycle review.

"This was the most complex product we've taken to launch. Not only the development, the dose counter and the single-cycle review, but also working through multiple customer touch points, from feasibility groups to supply chain management," said Hart. "It was certainly a challenge, but we successfully walked the path together and helped commercialise our client's product."

RESULTS

This project represents the latest in a long line of commercialisation successes from 3M's product commercialisation team. Not only did 3M develop, scale-up and commercialise a new formulation, it also developed and scaled-up a significant piece of additional technology at the same time – the 3M™ Integrated Dose by Dose Counter. With its ability to manage a complex supply chain, including multiple new suppliers, 3M never missed a milestone, and dedicated commercialisation managers provided a single point of contact for the client. With outstanding collaboration and a long history in MDI development and commercialisation, 3M was able to help its client effectively introduce a successful new product.

KEY SUCCESSES

- Achieving a single-cycle review for new-to-the-world product
- Solving formulation challenges that puzzled pharmaceutical companies in the past
- Introducing the 3M™ Integrated Dose by Dose Counter
- Managing complex global supply chains and schedules
- Building a stronger working relationship with our client.

To learn more about 3M Drug Delivery Systems' solutions and services, visit www.3M.com/InhalationExpertise or call +1 800 643 8086.

> "This MDI product represented an ideal opportunity to introduce this specific dose counter to the market"

ONdrugDELIVERY

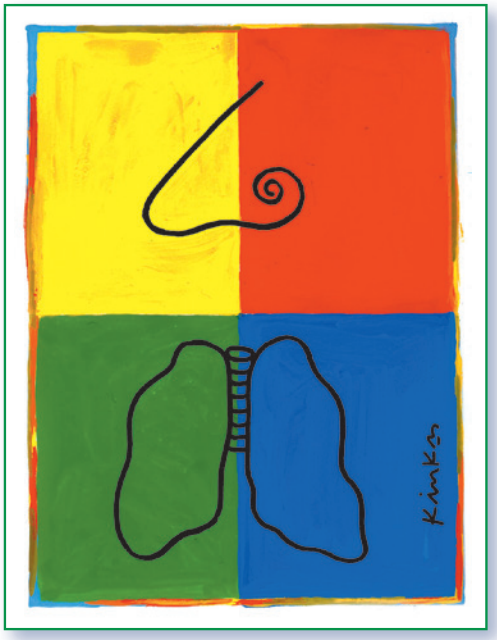
ONdrugDelivery 2015 EDITORIAL CALENDAR

Publication Month	Issue Topic	Materials Deadline
January 2015	Ophthalmic Drug Delivery	Closed
February 2015	Prefilled Syringes	January 12th
March 2015	Transdermal Patches, Microneedles & Needle-Free Injection	February 3rd
April 2015	Pulmonary & Nasal Drug Delivery	March 2nd
May 2015	Injectable Drug Delivery: Devices Focus	April 13th
June 2015	Novel Oral Delivery Systems	May 4th
July 2015	Wearable Bolus Injectors	June 1st
October 2015	Prefilled Syringes	September 7th
November 2015	Pulmonary & Nasal Drug Delivery	October 5th
December 2015	Delivering Biotherapeutics	November 9th

PLEASE MARK YOUR CALENDARS AND PLAN TO ATTEND!

RDD EUROPE 2015

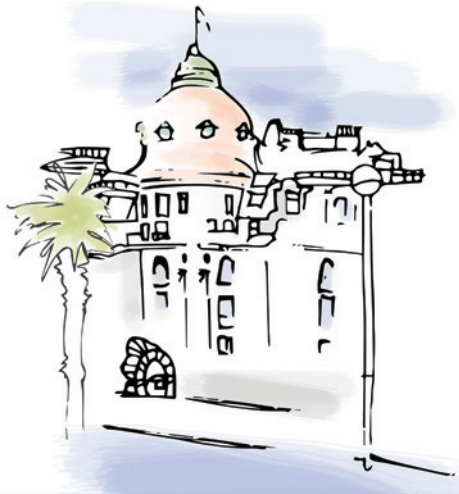
Respiratory Drug Delivery



MAY 5 - 8, 2015

Palais des Congrès d'Antibes

Nice, **FRANCE**



For more information visit www.rddonline.com/rddeurope2015

RDD Europe is a conference jointly organized by

RDD Online Respiratory Drug Delivery

Aptar pharma

Hovione

DESIGN OF COMPOSITE PARTICLES VIA SPRAY DRYING FOR DPI FORMULATIONS

In this article, Cláudia Moura, PhD Student; Eunice Costa, PhD, Scientist, Drug Product Development; Filipe Neves, PhD, Senior Scientist, Group Leader, Drug Product Development; all of Hovione, describe how composite formulations - API embedded in an excipient matrix - overcome the challenges in inhalation powder development, and make the case for spray drying as a highly suitable, tunable and scalable particle-engineering method for producing them.

INTRODUCTION

In order to deliver an active pharmaceutical ingredient (API) to the deep lung, it is generally recognised that the particles should have an aerodynamic particle size between 1 and 5 µm. However, such small particles are characterised by a high surface energy and are thus very cohesive, exhibiting poor flow and aerosol performance. In addition, API dosages are typically in the microgram range, requiring a bulking agent for metering and handling the product. In order to address these constraints, the size-reduced APIs are usually blended with an inert coarse carrier – lactose monohydrate is the most commonly used excipient in DPI formulations.

> "A thorough understanding of the SD process thermodynamics, atomisation conditions and fluid dynamics allows the scale-up of SD processes so that the particle properties are maintained"

The main challenge of lactose-ordered mixtures is to ensure a balance between the adhesion of the API with the carrier, necessary for a stable and homogeneous blend, and an adequate separation of the respirable API upon inhalation. Generally, the larger carrier particles impact in the mouth and throat with a significant amount of API still adhered to the surface, which limits the delivery efficiency of the platform. In addition, formulation development needs to minimise the impact of the intrinsic variability on API/carrier properties on the final aerodynamic performance. Finally, the platform cannot be generalised to sensitive molecules such as biotherapeutics that cannot be size-reduced through conventional milling technologies.

The development of composite particles, in which the API is embedded in an excipient matrix, overcomes some of these challenges since particle-particle interactions are normalised and uniformity is ensured by design. In addition, the strategy allows the delivery of high-dose drugs (milligram range) which cannot be processed into ordered mixtures.

COMPOSITE PARTICLES: FORMULATION PLATFORM

Recently, different composite particle approaches have been developed, including platforms that have led to commercial products, focused on essentially reducing cohesiveness and improving dispersibility of respirable powders.[1] Examples of such approaches include the preparation of porous particles (e.g. PulmoSpheres) or

Dr Eunice Costa
Scientist, Drug Product Development
E: ecosta@hovione.com

Dr Filipe Neves
Senior Scientist, Group Leader,
Drug Product Development
E: fneves@hovione.com

Cláudia Moura
PhD Student
E: cmoura@hovione.com

Hovione
Sete Casas 2674-506
Loures
Portugal

T: +351 21 982 9000
F: +351 21 982 9388

www.hovione.com

highly corrugated particles (e.g. PulmoSol) to reduce the number/area of contact points, or coating of particles with surface active agents such as lipids, fatty acids, surfactants or aminoacids to reduce the surface energy and/or triboelectrification.[1,2,3]

The choice of composition also takes into account the excipient toxicity and ability for providing physiochemical stability to the dosage form on storage. The enabling technology transversal for most of these engineered particles is spray drying (SD). The design of composite particles integrates both formulation and SD process parameters since the particle size, morphology and excipient/API distribution is dependent on the interaction between both.

As exemplified in Figure 1, increasing the fraction of a shell-forming agent on the particle composition, for fixed SD parameters, led to increasing surface roughness, which generally improves aerosol performance.[3] On the other hand, for a fixed composition, increasing the feed droplet size led to an increase in particle size (PS), with a potential impact on reducing the fine particle fraction (FPF), as determined through in vitro cascade impaction, and hence the lung deposited fraction.

SPRAY DRYING: ENABLING TECHNOLOGY

Spray drying is a widely used technique for processing a liquid feed, namely a solution, suspension or emulsion, into a free-flowing powder.[4] In SD, a liquid feed is atomised by a nozzle into a drying chamber in which a stream of hot gas (e.g. air or nitrogen) flash dries the droplets, forming particles which are collected downstream (Figure 2). It is particularly applicable for processing labile molecules, since the suspended or dissolved solids are subjected to evaporative cooling during particle formation and to short residence times.

Although spray drying has been well-established for over a century, only in the last two decades has SD become a technology of choice for pharmaceuticals manufacturing, particularly for preparing amorphous solid dispersions for improving oral bioavailability of drugs and pharmaceuticals for pulmonary delivery. Indeed, SD is an enabling technology for DPI formulation since it allows a superior level of control over the final particle attributes such as particle size distribution, density, surface roughness, morphology and residual solvents/moisture levels so that adequate stability, flow and aerodynamic properties of the bulk powder are achieved.

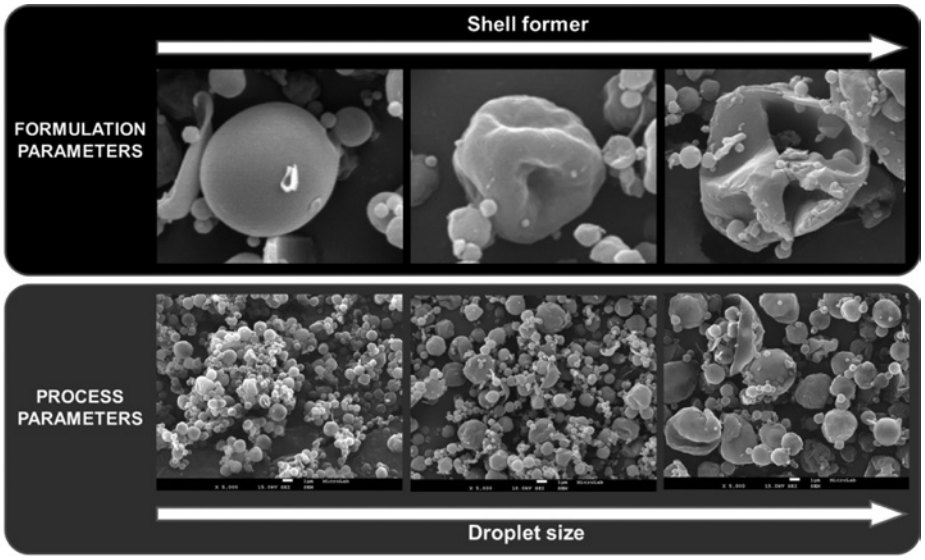


Figure 1: Formulation and process parameters impact on composite particle morphology.

Moreover, a thorough understanding on the SD process thermodynamics, atomisation conditions and fluid dynamics allows the scale-up of SD processes so that the particle properties are maintained across scales. On the other hand, SD is an energy intensive technique, which might be limiting in a cost perspective for processes with low solid throughputs, meaning trade-offs need to be well understood and optimised.

DEVELOPMENT APPROACH

The choice of excipients for developing composite particles by spray drying is rather limited, considering that few excipients are approved or well tolerated for inhalation. The design of a composite particle (see Figure 3) typically includes a shell in order to improve powder dispersibility, normalise particle interactions, confer a certain degree of API independence (for relatively low API fractions of the total composition), and potentially impose a moisture protection barrier for hydrophilic APIs.

The shell formers that can be explored include surface active ingredients that preferentially migrate to the droplet surface once formed at the SD atomiser tip or surround the API in lamellar/micellar structures, namely surfactants such as phosphatidylcholines (e.g. PulmoSpheres [5]), fatty acids and cholesterol. Another option is the use of hydrophobic aminoacids such as L-leucine. Due to its low solubility in aqueous feedstocks and fast crystallisation kinetics, L-leucine is expected to crystallise during droplet drying and subsequently to accumulate on the receding droplet surface.[6]

Depending on API solid state properties and on whether the API is solubilised or suspended on the feedstock, a glass-forming excipient may be required to stabilise the amorphous API (for a small molecule) or to prevent denaturation (for a protein), ensuring physical stability upon storage.

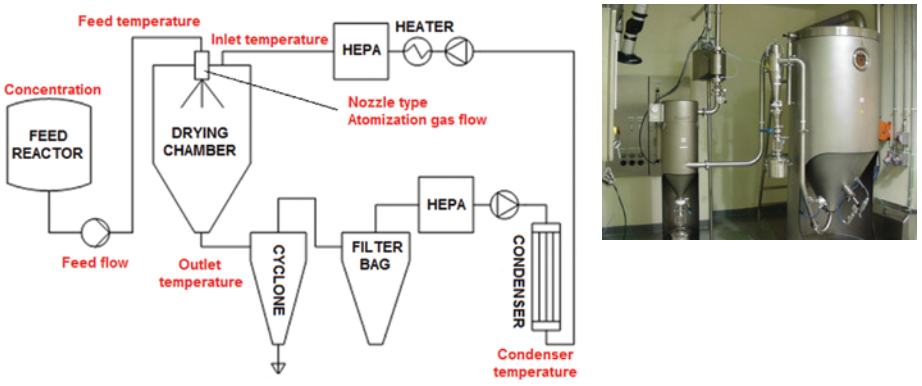


Figure 2: Spray drying apparatus: schematics with main operating parameters (left side) and picture of a GEA NIRO Mobile Minor unit (right side).

Glass stabilisation agents suitable for the application include carbohydrates such as mannitol, trehalose or raffinose, which are characterised by a high glass-transition temperature. The PulmoSol technology is an example of glass-stabilised formulation, used for insulin DPI.[6]

The SD feedstock composition can also include a pore-forming agent in order to increase the particle porosity and hence improve dispersibility through the increase in roughness and decrease in the density and number of contact points. Examples of porogens include high-vapour-pressure fluorocarbons, which can be included in the feedstock in the form of an emulsion (e.g. PulmoSpheres [5]), or volatile salts such as ammonium carbonate.[1]

Additional agents may also be required if the formulation includes a large biomolecule, namely buffering agents in order to maintain the native conformation of, for example, permeability enhancers and antioxidants.

Finally, the API can be incorporated in the amorphous state if solubilised in the SD feed or in the crystalline state if suspended in the SD feed. In the latter case, the API needs to be reduced to the nano-range in order to be successfully processed into a composite particle via spray drying.

The final particle size and morphology of spray dried composite particles not only depends on the selected (i) formulation composition, but also on feed properties such as (ii) solid concentrations and (iii) solvent compositions, on (iii) the resulting droplet size upon atomisation and drying conditions such as (iv) drying gas temperature and (vi) spray and drying gas patterns at the vicinity of the atomiser.[6] These parameters are very much interdependent since the droplet size is a result of the feed viscosity and surface tension, besides the actual nozzle design and atomisation gas flow (for a two-fluid nozzle, which is the typical choice for preparing inhalation powders). In addition, several different particle morphologies and relative component distribution across the particle can be obtained for a given droplet size. A universal description of the particle formation step is difficult to achieve, but general tendencies can be derived from the formulation components' Peclet number, Pe, as illustrated in Figure 4. The Pe number is a function of the ratio between solvent evaporation rate (k) and the diffusion coefficient of the given solute / suspended solid: $Pe \propto \frac{k}{D}$.

In general, for a Pe number smaller than 1, the diffusion of the dissolved or suspended solids is faster than the radial velocity of

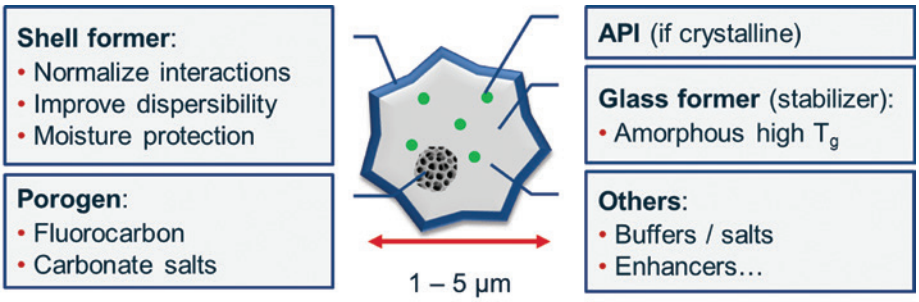


Figure 3: Composite particle design. The API can be incorporated in the engineered particle as crystalline nanoparticles or as an amorphous solid dispersion.

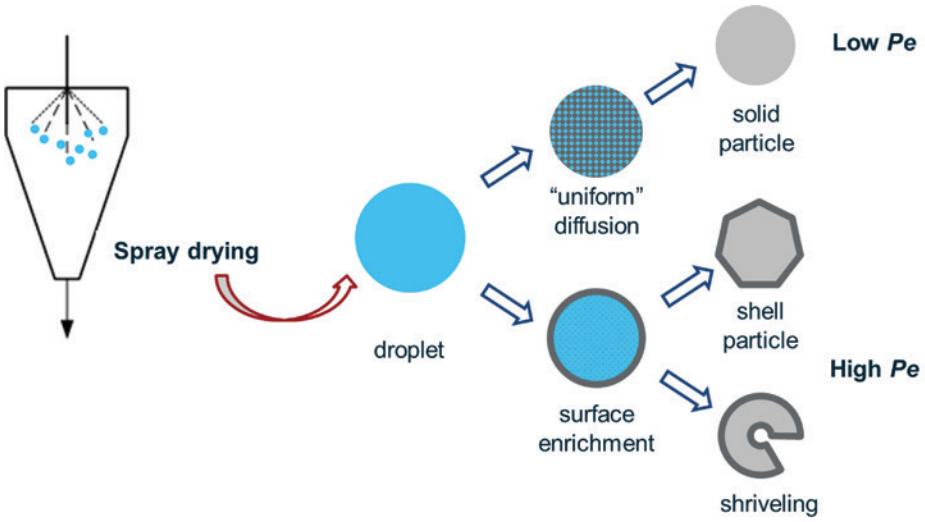


Figure 4: Development of composite particles results from integrating aspects of formulation and process design.

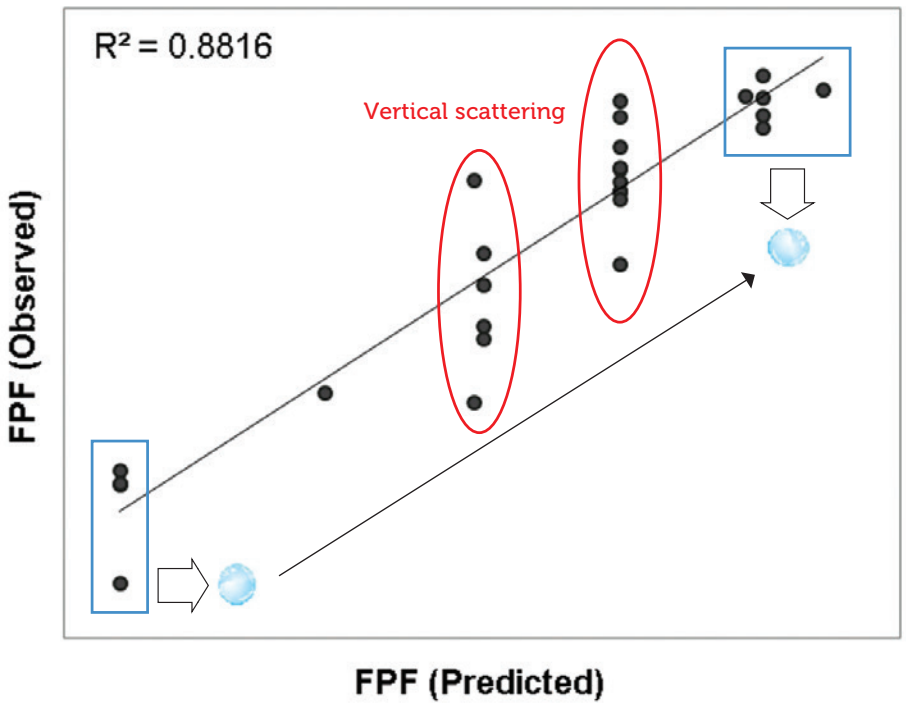


Figure 5: Statistical model for FPF with SD feed droplet related parameters as input factors. The in vitro aerodynamic performance was determined using a modified gravimetric Andersen cascade impactor.

the receding droplet upon drying. Hence, as shown on Figure 4, a solid uniform particle is expected. On the other hand, if the droplet surface recedes faster than the dissolved or suspended components diffusion, the surface will tend to become enriched in the component with higher Pe number. Depending on the shell properties, namely its solid state and mechanical properties, and droplet drying kinetics, hollow spheres or shrivelled structures can be obtained.

Given the complexity of the underlying mechanisms determining particle morphology and, ultimately, the composite particles aerodynamic performance, design of experiments (DoE) focusing on the main input factors can be a useful tool in expediting formulation and SD process optimisation, via derivation of local models for estimating final aerodynamic performance.

THE PRODUCT ANGLE: PERFORMANCE

The aerodynamic particle size is a function of (i) the geometric size of the particle, (ii) the shape/morphology and (iii) the density, these being the properties that can be manipulated for achieving a given aerodynamic performance. Following development studies based on DoE considering both formulation composition and SD operating parameters as input factors, it was observed that the FPF was mainly described by the factors determining the feed droplet size during SD within the explored ranges, as expected (Figure 5).

Although the FPF is fairly well described in Figure 5, there is significant vertical scattering on the observed FPF for a given predicted value. Upon closer inspection on the two main groups that present vertical scattering with a predicted FPF difference of about 10%, a statistical model was derived for the FPF as a function of input factors related with formulation parameters, which is able to capture well the differences on the observed FPF, as shown in Figure 6. This example shows that the relative impact of particle size

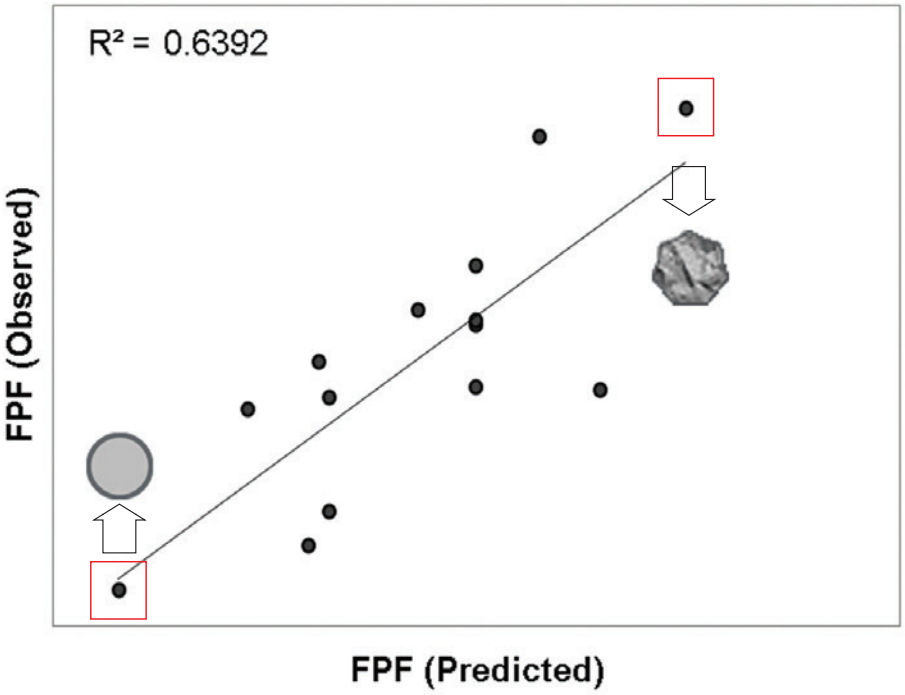


Figure 6: Statistical model derived for describing Figure 5 vertical scattering, using only formulation parameters as input factors; the relatively low R^2 can be explained by the intrinsic analytical method variability during FPF determination and the narrow range of variation of this one (the vast majority of the points show a prediction error of less than 5% of FPF).

is probably similar to that of morphology, within the desired (high) FPF ranges.

THE PROCESS ANGLE: THROUGHPUT

In general, composite particle FPF is improved by decreasing the geometric particle size, which can be accomplished by smaller feed droplet size and/or suspended or dissolved solids concentration. A smaller droplet size might require a decrease in the liquid feed flow, while a smaller concentration translates into lower solids throughput / higher cycle time.

During optimisation of the SD process for composite particles manufacturing, trade-offs need to be considered between maximising aerodynamic performance and establishing a cost-effective SD process with good throughput. In addition, the flow properties of bulk powders tend to be poorer for smaller geometric particle size, which can also impact negatively the yield of the downstream DPI filling process (e.g. capsule filling, CF). Integrated models for FPF and process throughput, as shown in Figure 7, can be a useful tool to evaluate the sweet spot in regards to formulation and SD process parameters for the benefit of the overall design.

Once these trade-offs are evaluated, a target droplet size is determined. During SD process scale-up, one of the main chal-

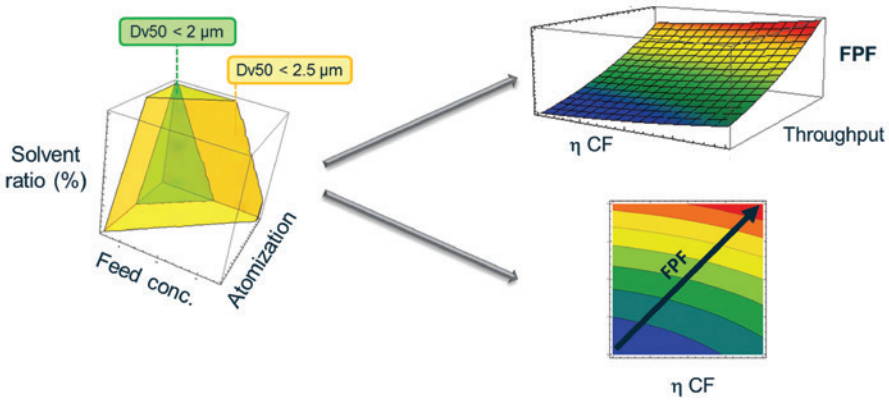


Figure 7: Trade-offs between process throughput and delivery efficiency (FPF).

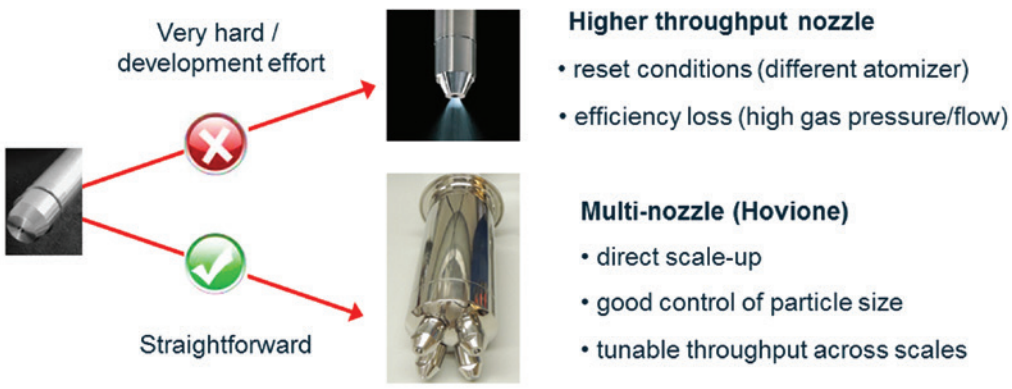


Figure 8: Scale-up approaches of SD processes, while maintaining droplet size.

lenges is to maintain equivalent droplet size across scales. Often the nozzle being used at a given scale needs to be abandoned as its operating ranges are exceeded and time-consuming testing needs to take place in order to select a new nozzle.

However, selection of a new nozzle is not always successful, as there are physical limitations on the atomisation of large liquid flow rates into very small droplets. A strategy to circumvent these constraints is to adopt a multi-nozzle apparatus of several "low liquid feed flow nozzles" (as opposed to a single high "liquid feed nozzle") so that the ratios between liquid and atomisation gas flow can be maintained in each nozzle.[8]

COMPOSITE PARTICLES: KEY ADVANTAGES & FEATURES

The principles described previously in regards to an integrated formulation and spray drying process development result in successful preparation of inhalable composite particles for DPI delivery. The main advantages and key features of composite particles are illustrated on the next sections.

DELIVERY EFFICIENCY

Composite particles are able to enhance significantly the delivery efficiency of DPIs in comparison to the traditional carrier-based approach, as API deposition on the mouth and throat tends to be greatly minimised. In Figure 9, the Next-Generation Impactor (NGI) data is shown for a standard lactose ordered mixture and a composite particles formulation both containing 0.4% w/w of API using a Plastiape HR model [7] device at 60 L/min, at a pressure drop of 4 kPa.[7] Similar emitted doses were observed with both formulations, but the FPF was more than tripled from 28% (CB) to an optimised value of 90% (CP).

PRODUCT INDEPENDENT AERODYNAMIC PERFORMANCE

Another potential advantage of the composite particles is the ability to have similar aerodynamic deposition profiles regardless of the incorporated API, as long as the composite particle is designed to accommodate different APIs. The maximum API load that can be incorporated without significantly impacting the aerodynamic performance should be evaluated case by case. Given that most inhaled APIs are delivered in very low dosages, this feature is a key advantage to be explored. The API-independence of the aerodynamic profile allows upfront formulation and process development in order to obtain composite particles with different aerodynamic behaviours, potentially targeting different areas of the lung. In Figure 10, it is shown that the same particle morphology and FPF is obtained for composite particles comprising only excipients (CP) and two different model drugs (CP1 and CP2).

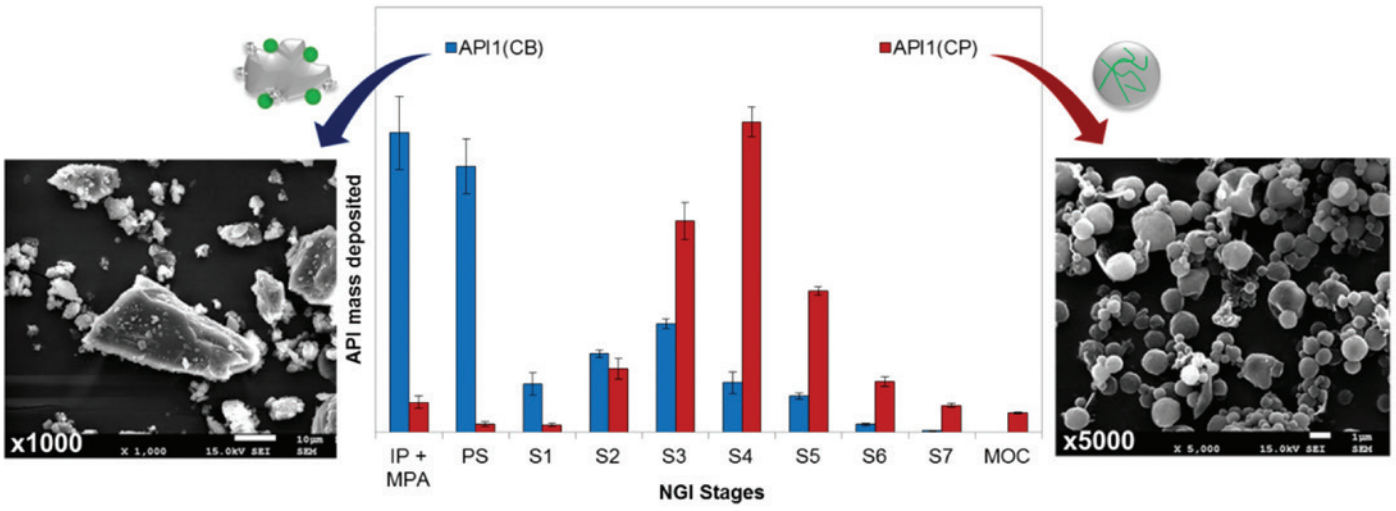


Figure 9: Aerodynamic performance of the CB (carrier based) and CP powder formulated with API model drug 1 (API1) by an NGI with chemical recovery at 60 L/min using a Plastiape HR device model 7 operated at 4 kPa, where MPA, IP, PS, S1 and MOC stands for Mouthpiece adaptor, induction port, pre-separator, stage 1 and micro-orifice collector respectively.

EVERYTHING FOR INHALATION

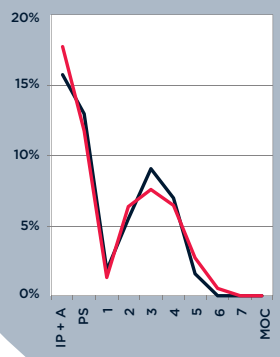
API PARTICLE REDUCTION

- Jet milling
- Wet polishing
- Composite particles
- Nanocoating
- Microencapsulation
- Spray drying

FORMULATION

- Pure API
- Carrier based
  - Lactose based
  - Leucine based
  - Mannitol based
  - Custom excipients
  - Engineered particles

MATCHING INNOVATOR DEPOSITION PROFILES



CAPSULE FILLING

- Phase I clinical trials (Fill gun)
- Phase II clinical trials up to low volume commercial - automated capsule filling (100% net weight unit verification)
- Blistering and packaging

Integrated Development and API Supply

Budesonide, fluticasone, formoterol, mometasone, salmeterol, tiotropium

Hovione

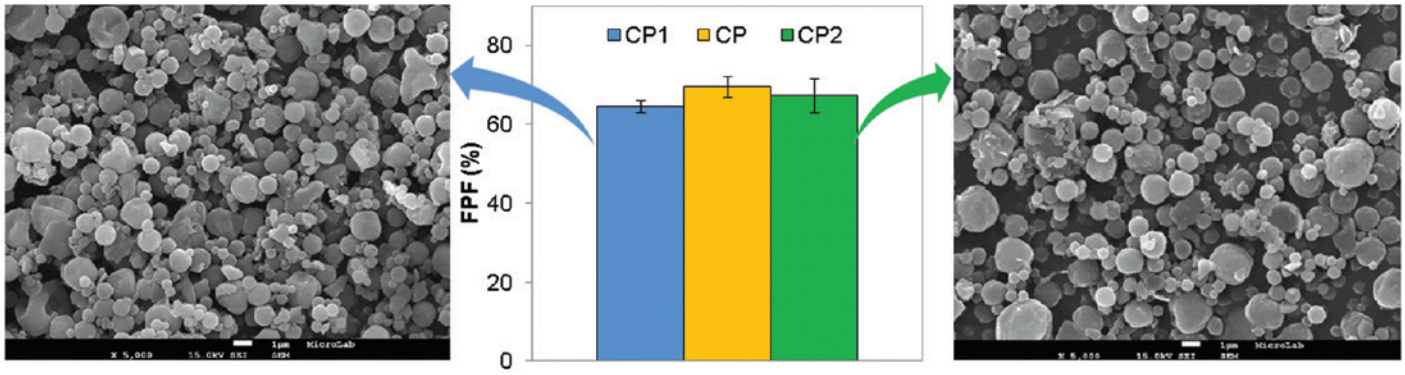


Figure 10: Fine particle fraction for composite particles "as is" and with two different APIs, where CP stands for composite particle "as is", CP1, composite particle containing API model drug 1 and CP2, composite particle containing API model drug 2 at low concentrations (< 5% w/w); scanning electron micrographs of the respective powders are also included.

STABILITY UNDER NORMAL PACKAGING CONDITIONS

Composite particles prepared by spray drying usually comprise partially amorphous materials: either the API, an excipient, or both. As mentioned previously, the inclusion of a glass-forming excipient, in a sufficient amount to ensure physical stability of the API, is typically required. In Figure 11 the stability study of composite particles containing a model inhalation API is shown. The stability upon storage under normal packaging conditions was assessed on both an aerodynamic performance and solid-state perspective, including characterisation through cascade impaction and XRPD. The FPF and solid-state form was reproducible at the different stability timepoints and conformal in comparison with both normal and accelerated conditions.

CONCLUSIONS

In the past two decades, a significant research effort has been focused on the design of carrier-free formulations for DPI formulations. In general, these formulations are based on sophisticated particle engineering technologies, requiring substantial know-how on both formulation and process design.

An integrated analysis of these two aspects is critical in order to develop a final system that (i) maximises lung delivery efficiency, while ensuring (ii) product long term stability through (iii) a scalable and economically viable particle engineering process.

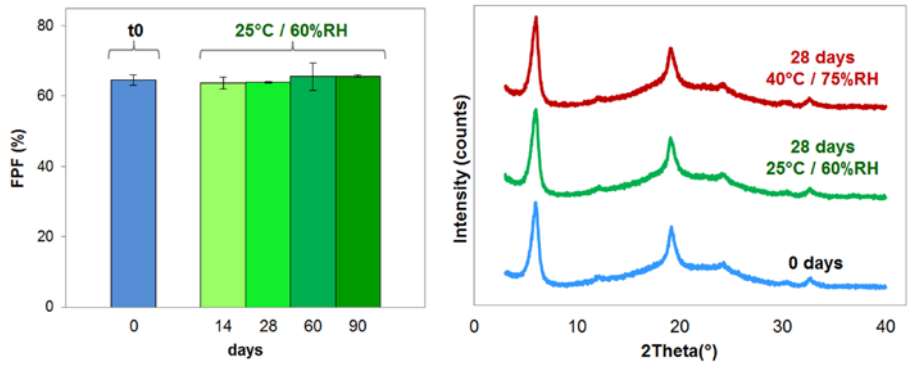


Figure 11: Stability over time of a composite particle containing an inhalation model drug. The (i) FPF and (ii) solid state via XRPD was assessed at 0 days, 14 days, 28 days, 60 days and 90 days. The capsules were conditioned in double aluminum foil and exposed to normal conditions of 25°C and 60% RH and at accelerated condition of 40 °C and 75% RH.

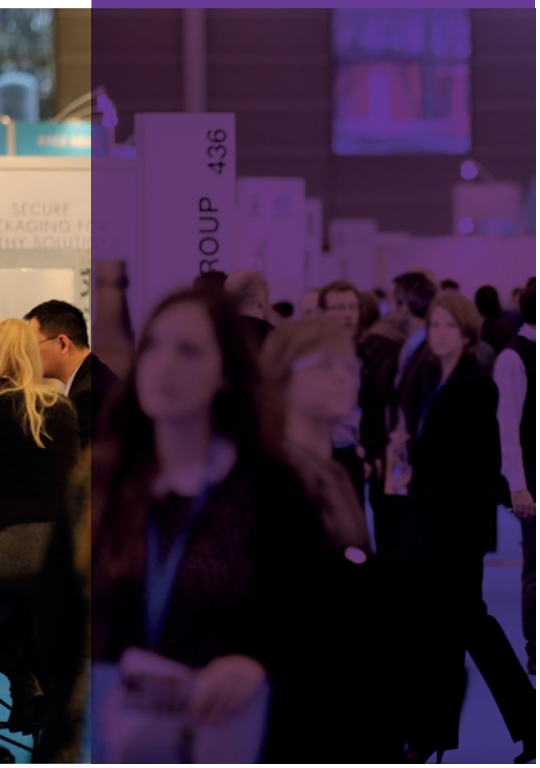
REFERENCES

1. *Hoppentocht M, Hagedoorn P, Frijlink HW, de Boer AH, "Technological and practical challenges of dry powder inhalers and formulations". Adv Drug Delivery Rev, 2014, 75C, pp 18-31.*
2. *Healy AM, Amaro MI, Paluch KJ, Tajber L, "Dry powders for oral inhalation free of lactose carrier particles". Adv Drug Delivery Rev, 2014, 75C, pp 32-52.*
3. *Chew NYK, Tang P, Chan H-K, Raper JA, "How much particle surface corrugation is sufficient to improve aerosol performance of powders?", Pharm Res, 2005, Vol 22, pp 148-152.*
4. *Masters K, "Spray drying – an introduction to principles, operational practice and applications". 1972 London: Leonard Hill Books.*
5. *Duddu SP, Sisk SA, Walter Y H, Tarara TE, Trimble KR, Clark AR, Eldon MA, Elton RC, Pickford M, Hirst PH, Newman SP, Weers JG, "Improved lung delivery from a passive dry powder inhaler using an engineered PulmoSphere powder". Pharm Res, 2002, Vol 19, pp 689-695.*
6. *Feng AL, Boraey MA, Gwin MA, Finlay PR, Kuehl PJ, Vehring R, "Mechanistic models facilitate efficient development of leucine containing microparticles for pulmonary drug delivery". Int J Pharm, 2011, Vol 409, pp 156-163.*
7. *Walzel P, "Influence of the spray method on product quality and morphology in Spray Drying". Chem Eng Technol, 2011, Vol 34, pp 1039-1048.*
8. *Neves F, Santos J, Olival L, "Multinozzle concept for expedite scale-up of spray dried inhalation powders". Provisional Patent PT107567.*
9. *Moura C, Vicente J, Palha M, Neves F, Aguiar-Ricardo A, Costa E, "Screening and optimization of formulation and process parameters for the manufacture of inhalable composite particles by spray-drying". Drug Delivery to the Lungs Conference, 2014 [Abstract] In Press.*

Drug Delivery & Packaging Pharmapack EUROPE

EXHIBITION & CONFERENCE **11&12 FEBRUARY 2015 PARIS EXPO, PORTE DE VERSAILLES, HALL 5**

Innovation, Networking & Education in Pharmaceutical Packaging and Drug Delivery Technologies



14th EDITION FEATURING:

- **370 international suppliers** in packaging and advanced drug delivery technologies
- **3,300 senior level managers** from pharma companies expected
- **2 day conference** to hear about the latest market trends for packaging developments and new drug delivery systems
- **1 day Technical Symposium** dedicated to Serialisation, Track & Trace
- **Workshops** allowing an in-depth discussion in 360° on specific technical issues
- **NEW!** **A learning lab** to enable visitors to learn how to apply new concepts or tools to their projects
- **Innovation Gallery** showcasing recently launched products, organised by product category
- **The Pharmapack Awards ceremony** rewarding the most innovative solutions

#pharmapackeu

INDUSTRY ARTICLES, NEWS, WHITEPAPERS & EVENT PROGRAMME ON **WWW.PHARMAPACKEUROPE.COM**

UBM

QUALITY BY DESIGN IN INHALATION PRODUCT DEVELOPMENT

In this paper, Carole Evans, PhD, Director, Inhalation, and Lei Mao, PhD, Manager, Inhalation, both of Catalent Pharma Solutions, explore the application and principles of quality by design in the development, manufacture and commercialisation of inhaled pharmaceutical products. Compared with other dosage forms, QbD has not often been applied to inhalation products but, the authors argue, the potential benefits are significant throughout the process.

INTRODUCTION

Quality by design, frequently referred to as QbD, is a buzzword not just in the pharma and other industries but also in design and development across a wide breadth of industries. The quality-by-design process builds quality in from the beginning of development and makes certain that this quality is maintained through statistical, analytical and risk-management approaches, rather than tested for it after the fact.[1] Quality by design requires that the drug developer begins to think about commercialisation right at the beginning of development.[2]

While there has been a lot of work and discussion of the application of quality by design to many other dosage forms, there has not been as much of a focus on inhalation dosage forms, e.g. pressurised metered dose inhalers (pMDIs) and dry powder inhalers (DPIs).

BUILDING QBD INTO THE DEVELOPMENT PROCESS

The implementation of quality by design has been a response to regulatory requirements and industry concerns in the pharma and biotech industries. The US FDA is working to put it in place, through its pharmaceutical cGMP initiative, and through international collaboration as part of the International Conference on Harmonization (ICH) (see Box 1).[3,4]

Quality by design has to start right at the very beginning of product development, by thinking about the quality target product profile (QTPP). This helps keep the objective of successful commercialisation in mind all the way through the development process.[2] The QTPP will capture the critical quality attributes some of which, such as dose, may be poorly defined early in development.

BOX 1: ICH GUIDELINES ON QBD

The ICH guidelines [4] suggest the following steps for pharmaceutical development encompassing quality by design:

- Defining a quality target product profile (QTPP), relating to quality, safety and efficacy; this needs to consider factors such as the route of administration, dosage form, bioavailability, strength, and stability
- Identifying critical quality attributes (CQAs) of the drug product, active pharmaceutical ingredient and excipients, as decisions over these could have an impact on product quality
- Evaluating and refining the formulation and manufacturing process, including the attributes and process parameters that could affect the quality control attributes
- Combining the enhanced understanding of the product and process with quality risk management to defining a control strategy, in order to ensure that products of the right quality are produced consistently

Dr Carole Evans
Director, Inhalation

Dr Lei Mao
Manager, Inhalation
T: +1 919 481 4855
E: info@catalent.com

Catalent Pharma Solutions
160 Pharma Drive
Morrisville
NC 27560
United States

www.catalent.com

Quality by design requires drug developers to understand how input materials, formulations and processes can vary; how a product's critical quality attributes (CQAs – see Box 2) are related; and how the treatment's clinical properties are affected by any changes in the CQAs.[1] Selecting the right critical quality attributes is an important step in implementing a quality-by-design strategy. Defining the operation range or "design space" (see Box 2) of those variables to ensure consistent CQAs and control the product quality through lifecycle management is the ultimate goal for the quality-by-design concept. If the design space is large enough to encompass the input parameters that generate product not meeting the target product profile, an operation range may be defined in the design space that encompasses the range over which product may be reliably made. This can be evaluated by exploring a wide process range in order to establish the failure points.

QBD IN INHALATION PRODUCT DEVELOPMENT

When looking at quality by design during the development of an inhalation product (or for any form of drug product), it is essential to start by understanding the input materials, formulation, container closure systems, and process variables, and how these affect the critical quality attributes and therefore the finished product's performance within the design space.

The operating space is used to define the range for the process variables in quality by design, so that companies can be comfortable that performance is assured when the variables remain within the range. Any processes that link to the drug product manufacturing process, such as those controlling the physicochemical properties of the input drugs / materials, or functional packaging components and secondary packaging, will also need to have their own design space. Typically, inhaled products such as pMDIs and DPIs will have multiple design spaces requiring definitions and knowledge spanning API manufacture, formulation processes, filling and finally packaging.

There are a number of variables and factors that companies wishing to apply quality by design to inhalation product development need to take into account, and these all need to be assessed to consider their impact on the overall performance. See Box 3 for suggestions. There are likely to be other factors involved and these need to be considered on a case-by-case basis.

BOX 2: CQA, DESIGN SPACE AND QTTP

According to the ICH guidelines, a critical quality attribute or CQA "is a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality".[4]

A design space is the "multidimensional combination and interaction of input variables (e.g. material attributes) and process parameters that have been demonstrated to provide assurance of quality".[4]

The critical quality attribute is a subset of the quality target product profile.[2]

Using the input drug in a suspension MDI or DPI product as an example, the particle size distribution is critical and the finished product performance can only be assured when the drug particle size distribution is well controlled within a certain range (design space). An understanding of the size reduction/control processes and the post-manufacturing conditioning procedures, and their effect on other physicochemical properties of the drug substance, is equally important as these properties could have a significant impact to the finished product performance or stability. All these variables need to be evaluated in the quality-by-design studies during the product development phase in order to create and populate a robust database. This will help to understand the design space and justify the selected operating range.

Likewise, variables in the process, such as the mixing speed and time required for the dry-powder blend formulation manufacturing, need to be evaluated, and their impact on the key product performance needs to be well understood. This includes requirements such as consistently-delivered doses, as well as the desired aerosolisation performance parameters, which are typically determined

> "While there has been a lot of work and discussion of the application of QbD to many other dosage forms, there has not been as much of a focus on inhalation dosage forms."

BOX 3: SELECTION OF SUGGESTED RELEVANT VARIABLES & FACTORS IN APPLYING QBD TO OIDPS

Input drug substances applicable to all inhalation dosage forms:
- Particle size distribution, size reduction process, material conditioning

Pressurised metered dose inhaler:
- Drug/surfactant/co-solvent concentration, propellant ratio (if required)
- Excipient functionality
- Container closure variants
- Order of drug/surfactant/co-solvent addition
- Suspension agitation/homogenisation/recirculation time
- Process temperature/filling to exhaustion
- Process duration/disruption

Dry powder inhaler:
- Drug/carrier ratio, ternary cleaning agent and ratio (if required)
- Excipient functionality
- Blending process – speed and time
- Bulk formulation holding/conditioning
- Filling process variables
- Environmental control

Figure 1: ICH Q8(R1) Pharmaceutical Development; ICH Q9 Quality Risk Management; and ICH Q10 Pharmaceutical Quality System, all contribute to the principle of QbD.

by fine particle dose/fraction and mass medium aerodynamic diameter (MMAD). Building quality-by-design elements into the scale-up process also allows better definition of a robust process design space.

GENERAL APPROACH FOR QBD STUDY

Similar to other dosage forms,[3,4] creating a quality-by-design-based process for inhaled product development is complex, as there are many different variables in the drug development and manufacturing process. The overall approach is based on the risk assessment/management process, which involves:

a) initial risk assessment of the effects of those discussed variables on the CQAs based on the experience with similar products
b) study design and execution to evaluate the effect of the input variables on the CQAs
c) data analysis and trending to understand the correlation between the input variables and CQAs over the design space and
d) finalising the risk assessment and defining the operating space based on the outcomes of the experiments.

In terms of the quality-by-design experiments, a full factorial design is a powerful tool to capture all elements. This process, however, can be labour intensive, lengthy, and not very cost-effective. Partial factorial design approaches allows developers to understand the design space. Additional experiments may be required for a fuller understanding of any interaction effects identified in the initial designs. An alternative approach, such as an evaluation of the extremes of any combination effects could also be considered in the study design.

Once the effect of the process variables on the CQAs is understood, it's possible to evaluate the extremes of the combination effects. As shown in Figure 2, if the CQAs are affected by the energy input in mixing, the batches manufactured can be evaluated with the lowest and highest energy inputs. If both batches demonstrate consistent CQAs, a design space can be defined for all three elements, i.e. agitation/homogenisation speed, time, and energy (ranges between the lowest energy and highest energy input points).

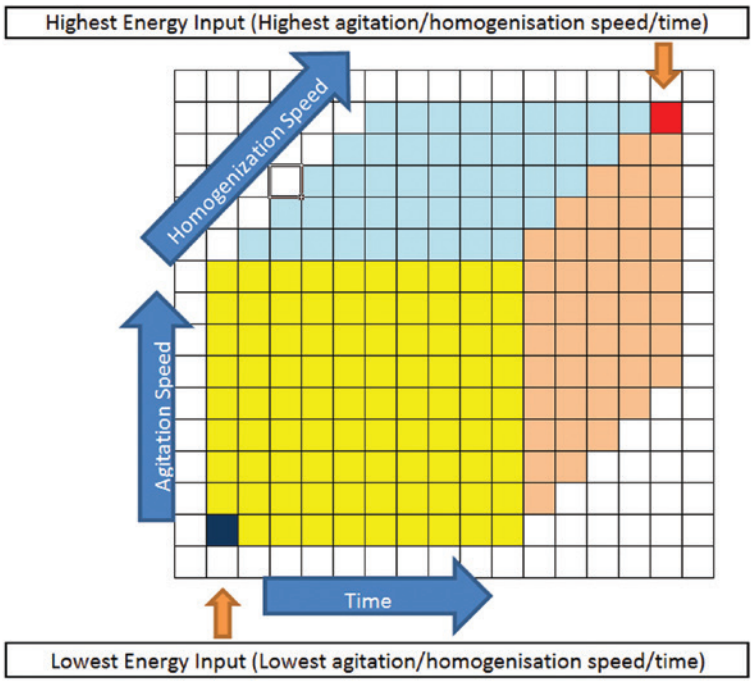


Figure 2: Study design based on the extremes of the combination effect.

CONCLUSIONS

Quality by design builds quality in from the product development phase, making commercialisation a focus. This ensures that the inhaled products maintain quality, safety, and efficacy, and keeps the production process as cost-effectively as possible. Successful quality by design relies on a full understanding of the effects from input materials, formulations, container closure systems, and process variables on the CQAs of the products. Proper study design and execution allows us to define the design space of all variables that can be controlled during product manufacturing. Quality by design ensures product quality through data driven risk assessment and product lifecycle management.

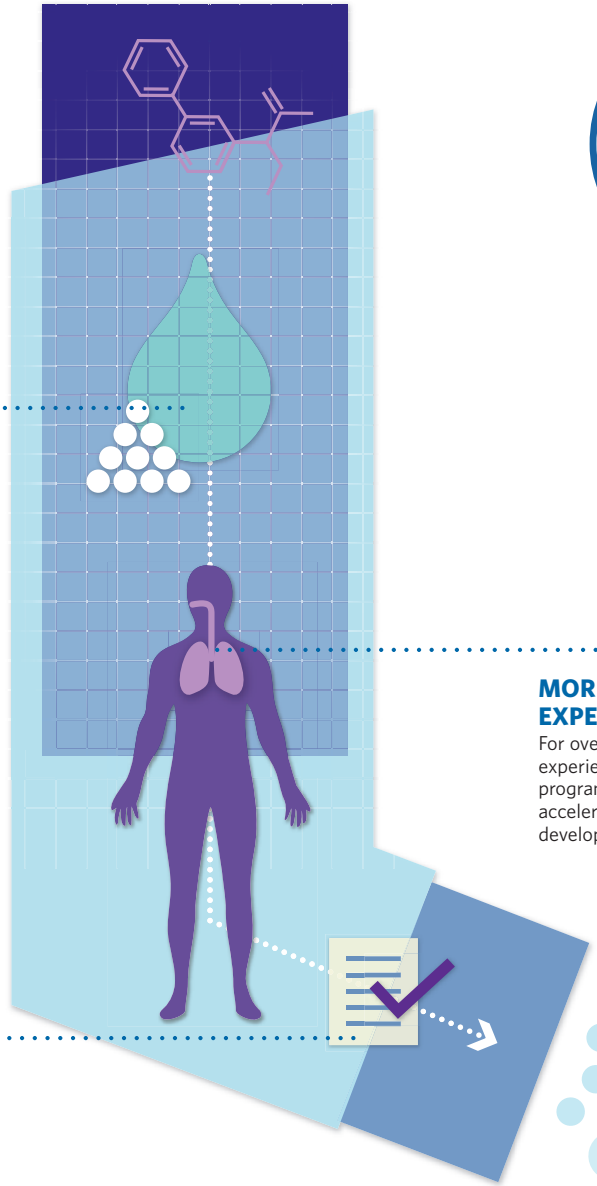
REFERENCES

1. *Rathore, AS & Winkle H, "Quality by design for biopharmaceuticals". Nature Biotech, 2009, Vol 27(1), pp 26-34.*
2. *"Quality by Design for ANDAs: Immediate-Release Dosage Forms. An Industry-FDA Perspective FDA/GPhA Workshop Draft Example Product Development Report". US FDA, May 4-5, 2010.*
3. *"Pharmaceutical cGMPs for the 21st Century — A Risk-Based Approach: Second Progress Report and Implementation Plan". US FDA, August 17, 2009. (Available from: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing.*

broadest inhalation capabilities. proven results.

Catalent® inhalation

CTLT LISTED NYSE



BROADEST DEVELOPMENT CAPABILITIES
With our complete range of dosage forms and comprehensive, integrated services, we create customized solutions that ensure superior results.

MORE INHALATION EXPERIENCE
For over 20 years, our deep experience and effective program execution have accelerated inhalation drug development time to market.

PROVEN TRACK RECORD
Our global project and supply chain management capabilities and proven regulatory expertise ensure high quality service and on-time delivery.

Breathe easier. Whatever your dosage form—pMDI, DPI, nasal, solution/suspension, or nebulizer—we are the catalyst for your success. With our broad range of services and deep industry experience, we create customized inhaled drug development and filling/manufacturing solutions that improve the value of your treatments from early stages to launch. And, our thorough understanding of regulatory requirements and submission protocols ensure ongoing, reliable supply. **Catalent. More products. Better treatments. Reliably supplied.™**

DEVELOPMENT DELIVERY SUPPLY

Discover more solutions with Catalent.
Call: + 1 888 SOLUTION (765 8846) Europe: 00800 88 55 6178
Email: solutions@catalent.com Visit: www.catalent.com

COMPANY PROFILE: NEMERA

Nemera

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

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

NEMERA'S INNOVATION CENTRE

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

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

Patient Insights & Human Factors Studies
Technical expertise and patient usability always work hand-in-hand. Along with the many fields of technological expertise (like material, mechanical and manufacturing engineering, mathematical models and other), creative design and usability assessment including Human Factors (HF) studies, are central to product development. The Innovation Centre carries real-world evaluations, through impartial volunteers and collects user feedback. Sophisticated technologies, like fast-camera tracking, give engineers an inside view of the way the device is used, making it safe and accurate for the patient.

Proprietary Devices & Contract Development
We apply the same quality-oriented process to the development of proprietary devices and to customised solutions under contract with laboratories. The development quality team guarantees full compliance not only of the final device but of all the development chain. Strong programme management ensures that the project is delivered on time and within budget.

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

NEMERA IN FIGURES

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

A WORLD LEADER IN DRUG DELIVERY SOLUTIONS

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

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

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

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

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

Contact:

Laurence Quesdeville
Communication Manager
T: +33 1 57271317
E: information@nemera.net

Nemera
118 avenue de France
75013 Paris
France

www.nemera.net

Advancia® is a new range of preservative-free nasal spray pumps

Figure 2: Advancia® user independent and preservative free nasal spray pumps.

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

Ophthalmic

Preservatives are harmful to patients' eyes and may jeopardise adherence to treatments, therefore Novelia® is the user friendly, preservative-free eye dropper with a precision blue tip.

Dermal/Transdermal

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

A NEW NAME THAT STANDS FOR LIFE & EFFICIENCY

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

Nemera CEO Marc Haemel commented: "Today, an exciting new adventure begins. I am very pleased to introduce you to Nemera, our new company name. We work hand-in-hand with pharmaceutical companies to design, develop and manufacture the drug delivery devices that help patients every day.

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

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

Find Nemera on the web at: www.nemera.net

PROTECTING INHALATION DRUG DELIVERY DEVICES WITH PARYLENE CONFORMAL COATINGS

Set against the backdrop of an innovative and rapidly growing inhalable drug delivery device sector, Dick Molin, Senior Medical Market Specialist, Specialty Coating Systems, Inc, describes applications of Parylene coatings as protective barrier coatings in inhalable drug delivery devices, and the detailed characteristics of Parylene which make it particularly suited to these applications.

Inhalers of various types have been in use for decades, long before the days of modern drug delivery devices. In fact, inhalers and nebulisers are the most common way to deliver drugs to asthmatic lungs. Today, however, more compositions of drugs are being delivered using inhalation technology than ever before due to the discovery that many types of medications readily absorb through the alveolar region directly into blood circulation. These drugs reach beyond the standard pulmonary applications (e.g. asthma and other respiratory conditions) into treatments for various diseases and conditions, opening up additional treatment options for doctors and patients and creating a need for alternative device designs from medical manufacturers.

> "In some cases, device materials must be made biocompatible. In others, the device materials require barrier protection from the medicines that they are transmitting and/or the medications must be protected from any leachables in the device material itself"

Because lungs are capable of rapidly absorbing pharmaceuticals and have the capacity for overcoming first-pass metabolism, pulmonary delivery of drugs has become an attractive target and of tremendous scientific and biomedical interest in the healthcare research area. Delivering drugs via inhalation technology is not only convenient, it is advantageous to many patients as it typically requires a lower dose than the same drug when ingested. Inhalation drug delivery also has negligible side effects on the rest of the body, which can be particularly important for long-term patients as the whole body is not exposed to the drug on a regular basis. Therefore, along with asthma, this route is being developed to treat local infectious diseases, pulmonary hypertension, Parkinson's disease. However, when systemic (whole body) delivery is required via the lung, it is possible to formulate accordingly, and for such applications the pulmonary route is used to deliver, for example, insulin for diabetes, growth hormones and oxytocin, to name only a few.

TRADITIONAL INHALER TECHNOLOGIES

Metered-dose inhalers (MDIs) are the most common asthma medication delivery systems used. They deliver a specific amount of medication to the lungs, in the form of a short burst of aerosolised medicine that is usually self-administered by the patient via inhalation. It is the most commonly used

Mr Dick Molin
Senior Medical Market Specialist
T: +1 317 451 8549
F: +1 317 240 2739
E: dmolin@scscoatings.com

Specialty Coating Systems, Inc
7645 Woodland Drive
Indianapolis
IN 46278
United States

www.scscoatings.com

delivery system for treating asthma, chronic obstructive pulmonary disease (COPD) and other respiratory diseases.

Dry-powder inhalers are available for specific medications, including beta2-agonists and corticosteroids. Though they work similarly to MDIs, unlike breath-actuated MDIs, the patient must inhale rapidly. After inhaling deeply, the patient holds his or her breath for 10 seconds.

Nebulisers can be used with all classes of inhaled medications but are most commonly used with short acting beta2-agonists and ipratropium bromide. The medication is placed in a chamber that is connected to a mains or battery powered air compressor. The compressor blows air through the chamber, atomising the medication so the patient can inhale it through a mouthpiece or facemask. While several variations of nebulisers exist, the one key advantage of this type of system is that it requires no hand-breath coordination on the patient's part.

NEXT-GENERATION TECHNOLOGIES

The market for all types of inhaled medications is changing rapidly. According to the latest reports from BBC Research, the global pulmonary drug delivery technologies market, which was US$19.6 billion (£12.5 billion) in 2010, is projected to reach nearly $44 billion by 2016 at a compound annual growth rate (CAGR) of 14.3%. MDIs, together with the the infusion systems market, will be the largest drug delivery device segments, accounting for more than 96% of total revenues. The global drug delivery device market will be driven by new technological advancements, as further emphasis is placed on needle-free technology, and the adoption of cost cutting measures in the infusion system market (e.g. increased automation).

Several device manufacturers are well on their way to expanding the inhaler market with new, innovative devices that deliver "non-traditional" medications in order to treat a host of diseases and conditions. One leading-edge application delivers insulin to diabetics via an inhalation device, eliminating the need for multiple daily injections. Another non-respiratory innovation provides a self-administered, adjunctive, as needed, inhaled treatment option for Parkinson's disease, to be used in conjunction with traditional oral medication.

> "Parylene ... is not applied to surfaces by dispensing, dipping, brushing or spraying – it literally "grows" on the receiving surface"

Like all other areas of medicine and patient care, drug delivery devices are also moving toward total interconnectivity. "Smart" devices can be beneficial to track frequency of device use (e.g. date and time), symptom tracking, medication levels, etc, in a way that can be downloaded to a patient's smartphone, tablet or PC and/or transmitted to a physician for symptom monitoring and subsequent treatment changes. As the market continues to advance in this direction, protection of electronic components will be critical.

With inhaler technology stepping into the area of more complex drug delivery and incorporating the latest in seamless remote transmission capabilities, requirements are increasing with regard to protection. In some cases, device materials must be made biocompatible. In others, the device materials require barrier protection from the medicines that they are transmitting and/or the medications must be protected from any leachables in the device material itself. Still other applications require that the moving components be able to glide smoothly, ensuring even drug distribution.

These, and more, are common reasons that device manufacturers look to conformal coatings. The challenge is determining what coating can reliably offer the properties desired for a given device without adding significant dimension or weight, while also being able to endure frequent use without consequence.

PARYLENE CONFORMAL COATINGS

A biocompatible conformal coating that can both protect and lubricate without adding significant dimension to a surface is Parylene. Parylene conformal coatings provide excellent barrier protection for internal and/or external areas of drug delivery devices. Parylenes are also highly lubricious, and as hydrophobic materials, minimise adhesion of liquid, mist or dry medication to the internal parts of the inhalation device.

Parylene is the generic name for a unique series of chemically-inert, polymeric coatings. Several variants of Parylene exist to suit a variety of applications. All are free of fillers, stabilisers, solvents, catalysts and plasticisers. As a result, the Parylenes present no leaching, outgassing or extraction issues.

What makes Parylene different from other protective coatings is that it is not

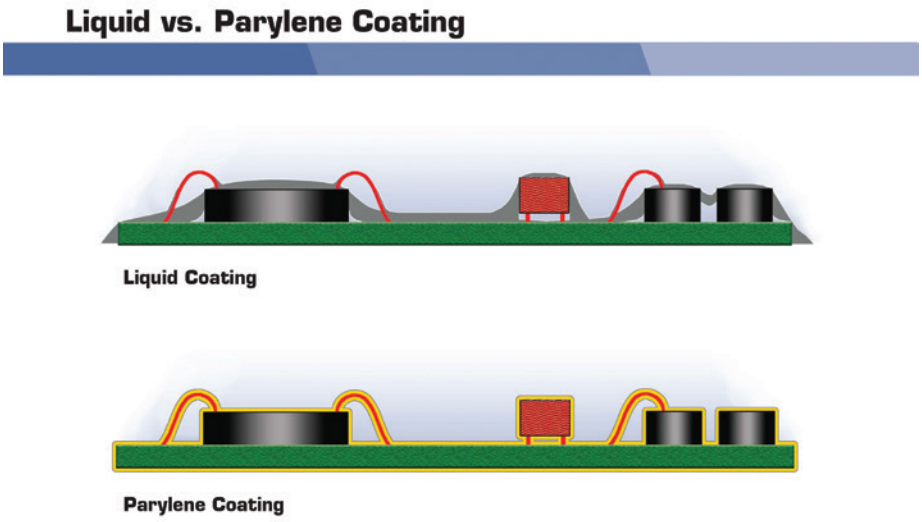


Figure 1: Illustration of the difference between a liquid coating and a Parylene coating.

applied to surfaces by dispensing, dipping, brushing or spraying – it literally "grows" on the receiving surface in a vapour deposition polymerisation process. Parylene adds no perceptible dimension or weight, and not only protects but enhances substrate properties as well.

Parylene coatings are applied in a vacuum deposition polymerisation process in which devices are placed in a room-temperature deposition chamber. The powdered raw material, known as dimer, is placed in the vaporiser at the opposite end of the coating system. The double-molecule dimer is heated, sublimating it directly to a vapour. The dimer vapour is then heated to a very high temperature that cracks it into a monomeric vapour. This is then transferred into an ambient temperature deposition chamber where it spontaneously polymerises onto all surfaces, forming the ultra-thin, uniform and extremely conformal Parylene film.

The entire Parylene coating process is carried out in a closed system under a controlled vacuum. The deposition chamber and items to be coated remain at room temperature throughout the process and no additional curing process or steps are required. The molecular "growth" of Parylene coatings ensures a uniform, conformal coating at the thickness specified by the manufacturer. Additionally, because Parylene is formed from a gas, it penetrates into every crevice, regardless of how seemingly inaccessible, ensuring complete encapsulation of the substrate without blocking or bridging even the smallest openings (see Figure 1).

Parylene's unique deposition process allows the polymer films to be formed in thicknesses ranging from several hundred angstroms to 75 µm. These ultra-thin coatings are well suited for medical devices that continue to shrink and become more complex in nature.

Biocompatibility and Biostability:
Parylenes N, C and Parylene HT® comply with biological testing requirements per ISO-10993. Testing includes cytotoxicity, sensitisation, intracutaneous reactivity, acute systemic toxicity, implantation (2, 12 and 26 weeks), haemocompatibility (haemolysis and PPT) and pyrogenicity. SCS Parylenes N, C and Parylene HT are also certified to comply with the biological testing requirements for USP Class VI Plastics.

SCS Parylene Properties

		Parylene N	Parylene C	Parylene HT	Silicone (SR)	Polyurethane (UR)
Water Absorption (%)		<0.1	<0.1	<0.01	0.1	0.6–0.8
Gas Permeability @ 25°C cc•mm / m²•day•atm	N_2	3.0	0.4	4.8	—	31.5
	O_2	15.4	2.8	23.5	19,685	78.7
	CO_2	84.3	3.0	95.4	118,110	1,181
	H_2	212.6	43.3	—	17,717	—
Coefficient of Friction	Static	0.25	0.29	0.15	—	—
	Dynamic	0.25	0.29	0.13	—	—
Rockwell Hardness		R85	R80	R122	40A–45A (Shore)	68A – 80D (Shore)
Tensile Strength		7,000 psi	10,000 psi	7,500 psi	350 – 1,000 psi	175 – 10,000 psi
Thermal Usage w/o Breakdown	Continuous	60°C	80°C	350°C	260°C	121°C
	Short-Term	80°C	100°C	450°C	—	—
Penetration Ability*		40 x dia.	5 x dia.	50 x dia.	Dip or Brush	Dip or Brush
Dielectric Strength @ 1 mil.		7.0KV	5.6KV	5.4KV	2.0KV	3.5KV
USP Class VI Polymer		Yes	Yes	Yes	Not All	Not All

*Depth into tubing and crevices.

Note: For test methods and sources, see the SCS Parylene Properties brochure.

Figure 2: Summary specifications and properties of Parylene.

"Because Parylene is formed from a gas, it penetrates into every crevice, regardless of how seemingly inaccessible, ensuring complete encapsulation of the substrate without blocking or bridging even the smallest openings"

Barrier Properties:
Parylene coatings are excellent moisture and chemical barriers for medical device components. Applied much thinner than alternative coatings, Parylene provides a pinhole-free barrier to protect against medications, moisture, chemicals and common gases.

Dry-film Lubricity:
Parylene coatings offer a low co-efficient of friction, nearing that of polytetrafluoroethylene (PTFE), ensuring that device components move smoothly to enhance patient comfort and ensure even delivery of medication.

Dielectric Properties:
Parylenes have excellent dielectric properties as they can be formed as thin, continuous films, free from defects and fillers, the latter of which are commonly found in conventional coatings. Parylene coatings have low dielectric constants and dissipation factors, and high dielectric strengths, enabling electrical and communication signal transfer without absorption or loss of signal strength.

RF Properties:
As electronics used in medical devices continue to advance, they are often required to operate reliably at higher frequencies than their predecessors. Some materials, however, lose some of their key performance properties when they are subjected to high frequency ranges. It has been demonstrated that Parylene coatings do not experience a reduction in dielectric constant or dissipation factor properties under high frequency (6 GHz) conditions. Thus, they are well suited to protect devices that operate in these ranges.

Other properties and specifications for Parylene are summarised in Figure 2.

CONCLUSION

The use of inhalers is an extremely efficient method for dispensing drugs. With the market expanding from using inhalers only in respiratory indications to using them for other indications and even to disperse drugs systemically for a wide range of conditions and diseases, it becomes even more essential to protect both the dispensing device and the medication being dispensed. While convenience and safety aspects drive this market, particularly in the area of patient home use, successful drug delivery devices must ensure that the medication remains stable during storage and use, the dose is evenly dispersed and, if applicable, data is effectively communicated from the device. Parylene conformal coatings offer device designers a proven option to enhance reliability and ensure the success of the latest in drug delivery technologies.

SONIC NEBULISATION IN RHINOLOGY

Chronic rhinosinusitis (CRS), a common condition affecting hundreds of millions of people worldwide, is often treated with saline solution or corticosteroids. In this paper, Laurent Vecellio, Ing, Phd, Scientific Director, and Sandrine Le Guellec, Ing, Scientist, Biology & Medical Research, both of DTF's Aerodrug division, and Gilles Chantrel, Co-Chief Executive Officer, DTF Medical, describe a sonic nasal nebuliser that operates with an acoustic frequency of 100Hz, and clinical studies demonstrating its efficacy in the delivery of treatments for CRS.

INTRODUCTION

The human nose daily ensures air conditioning of inspired air, the first immune protection of the lower airway and olfactory functions.[1] For many years the nasal cavities have been considered as a route for drug administration, justified by positive attributes such as the rapid onset of clinical effects, no first-pass metabolism, non-invasiveness, the improvement of patient comfort and hence compliance.[2,3]

The development of intranasal therapeutics concerns three major fields of interest linked to pharmaceutical targeting: topical delivery, systemic delivery and, more recently, central nervous system delivery. Topical delivery allows high doses of medication to be administered in the target organ and minimises adverse effects.[4] The middle meatus, the maxillary sinuses and the ethmoid regions have been identified as important target sites for drug delivery to treat inflammation and infections in rhinology pathologies locally.[5] Vasoconstrictors, anti-histaminics and corticosteroids are delivered by nasal spray to treat nasal congestion (or obstruction) and nasal mucosa inflammation during acute or chronic rhinologic pathologies such as allergic rhinitis, rhinosinusitis and nasal polyposis.

However, the nasal sprays currently available on the market are limited by their formulations and technologies. The drug fraction delivered beyond the nasal valve is low,[6] and most deposited drug is rapidly removed by mucociliary clearance and eventually eliminated through the digestive tract. Furthermore, dose delivery to the target sites depends on many factors, such as nasal

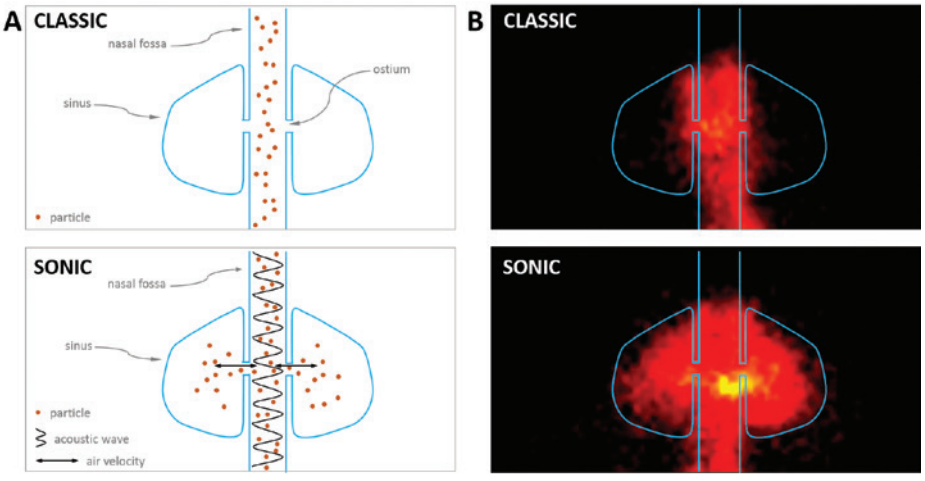


Figure 1: A. Sonic effect on ventilation and aerosol penetration in a sinus model acting as a Helmholtz resonator (SONIC versus CLASSIC). B. Influence of acoustic frequency waves on krypton gas penetration in human maxillary sinus (Scintigraphic imaging of front of nasal cavities of a healthy volunteer). (Adapted from Durand et al.[9])

Dr Laurent Vecellio
Scientific Director
Aerodrug
T: +33 2 47 36 60 61
E: laurent.vecellio@med.univ-tours.fr

Sandrine Le Guellec
Scientist, Biology & Medical Research
Aerodrug
T: +33 2 47 36 61 95
E: sandrine.leguellec@med.univ-tours.fr

AeroDrug
Aerosoltherapy R&D department of DTF medical
Faculté de médecine,
10 ter bd Tonnellé
37032 Tours
France

www.aerodrug.com

Gilles Chantrel
Co-CEO, DTF Medical
T: +33 4 77 74 51 11
E: gilles.chantrel@dtf.fr

DTF Medical
La Diffusion Technique Française
19 rue de la Presse,
42003 Saint Etienne
France

www.dtf.fr

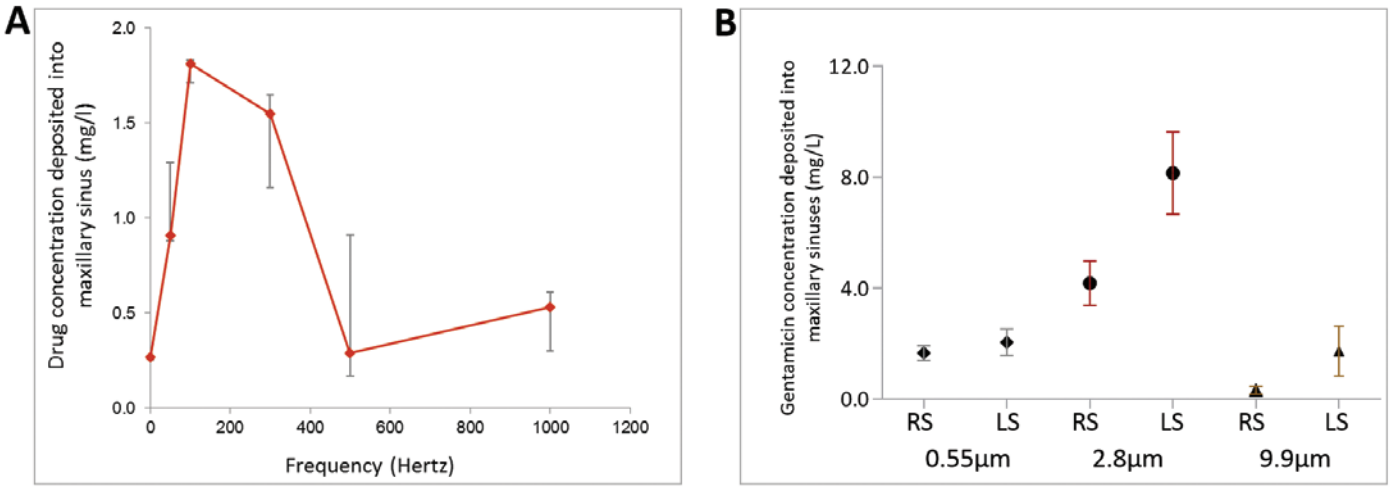


Figure 2: A. Effect of acoustic wave frequency on drug deposition in the maxillary sinuses of a nasal cast (mean±SD). (Adapted from Durand et al.[16]) B. Influence of the MMAD of the sonic aerosol on drug deposition in the right (RS) and left (LS) maxillary sinuses of a nasal cast (mean±SEM). (Adapted from Leclerc et al.[19])

plug penetration or orientation, resulting in considerable variability in terms of drug deposition and which may explain some failures in patient treatment.

Nebulisers produce finer particles than sprays (3 µm *versus* 30 µm) resulting in a more homogeneous drug deposition in the nasal cavities and improved targeting of the anatomic region of interest.[6,7] Adding an acoustic frequency enhances ventilation [8,9,10] and aerosol deposition [11,12] in the sinonasal cavities. Nebulisers are considered as medical devices, and drugs such as antibiotics, which are not available in nasal spray form, can be loaded in their reservoir.

There is no clear international recommendation for the use of nebulisers in rhinology,[4] but 45% of general practitioners and 78% of ENT specialists in France prescribe nebulisation for the treatment of upper respiratory tract diseases.[13,14]

SONIC NEBULISATION

The sinuses are air cavities connected to the nasal fossa by small openings (ostia). They are a source of local infection and thus a target zone for drug delivery. Due to their anatomy and poor ventilation, drug access is difficult.

In 1959, Guillerm and Badre [15] demonstrated that aerosols can be diffused in the sinuses by adding a sound. The theory is based on the principle of the Helmholtz resonator, whereby the sinus with its ostium resonates at a natural frequency when the air is excited (like air in a bottle). Outside air acts like a piston and increases the ventilation and penetration of aerosol into the sinus to target the local infection (Figure 1). Durand *et al* [16] demonstrated that 100Hz is the optimal frequency for delivering drugs to the maxillary sinuses in a nasal cast model (Figure 2). The Atomisor NL11SN®, a sonic nebuliser developed by DTF Medical, uses this 100Hz sound with a jet nebuliser generating the aerosol (Figure 3). It is a breath-enhanced nasal jet nebuliser improving drug administration during patient inspiration and reducing drug leakage in ambient air during exhalation. It uses a two-prong nasal plug in a soft material allowing an airtight seal with the nostrils, ensuring good aerosol delivery, minimising noise, the treatment of both nasal cavities simultaneously, and patient comfort.

Figure 3: Nasal nebulisation with the sonic nebuliser (Atomisor NL11SN®).

INFLUENCE OF PHYSICAL PARAMETERS ON DRUG DELIVERY

The deposition of sonic aerosol into nasal cavities has mainly been studied using artificial models of human nasal cavities (nasal cast). Artificial ventilation can be added to the nasal cast in order to simulate the nebulisation therapy conducted by a patient inhaling and exhaling through the nebuliser. Plastinated head model [11] and epoxy nasal replica based on CT-scan [17] are currently the nasal casts that best represent human anatomy and have recently been validated as being able to predict human nasal aerosol deposition.[18] The influence of different parameters in these nasal casts on the deposition of sonic aerosols has been evaluated with radioactivity and chemical tracers and drugs.

Sonic aerosol performance has been studied to assess whether it can enhance the penetration of the drug into the maxillary sinuses. Indeed, several studies have demonstrated that the addition of a 100Hz sound during aerosol administration significantly increases the penetration and deposition of aerosol in the maxillary sinuses whatever the sinus anatomy.[8,9,11,19,20] Durand *et al* showed penetration of a radioactive tracer in the maxillary sinuses of a plastinated head model [8] and a three-fold increase of deposited gentamicin.[9, 20]

The deposition of inhaled aerosols is also influenced by the particle size produced by the nebuliser. Studies have been conducted

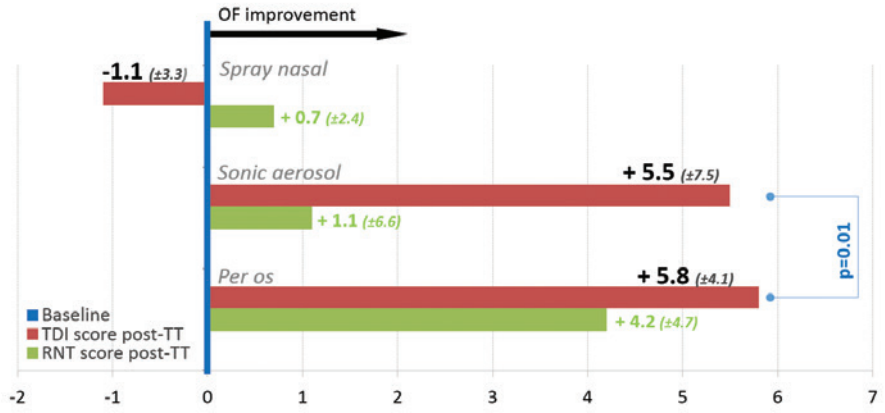


Figure 4: Score of olfactory functions (TDI and RNT scores) obtained from CRS patients before and after 16 days of corticotherapy with oral Medrol® (prednisolone), Pulmicort®, NL11SN® nasal sonic aerosol (budesonide), and Rhinocort® nasal spray (budesonide). (Adapted from Reychler et al.[22])

on nasal casts to determine the optimal particle size targeting different regions of interest.[17] A quantification of the fluorescein tracer deposited in each region was performed after nasal administration of aerosols with 2, 4.5, and 9.5 µm of mass median aerodynamic diameter (MMAD). With a constant inspiratory airflow rate (7 L/min), the aerosol mass deposited in the nasal cast increased with MMAD from 2.1% for the 2 µm aerosol to 43.5% for the 9.5 µm aerosol .

The increase in deposition was greater in the nose and nasal valve (+25% of deposition between 4.5 µm and 9 µm aerosols) than in the turbinate region (+8% of deposition between 4.5 µm and 9.5 µm aerosols). Deposition in the ethmoid was not affected by the increase in MMAD. A 2 µm MMAD aerosol can cross the nasal valve and produces more homogenous deposition in the nasal cavities.

The influence of particle size on aerosol deposition in the maxillary sinuses was investigated by Leclerc *et al*, who studied gentamicin deposition with an epoxy nasal replica and radioactive tracer deposition (SPECT-CTscan imaging) with a plastinated head model. They obtained optimal maxillary sinus deposition for the nebuliser generating a 2.8 µm aerosol with 100Hz sound, compared with results obtained with 9.9 µm, 0.55 µm, 0.23 µm aerosols with 100Hz sound. These studies demonstrate the interest of using a sonic nebuliser generating 2-2.8 µm of MMAD to target the anatomical regions of interest for treating rhinology pathologies (maxillary sinuses, ethmoid and turbinates).

Nasal deposition also depends on inspiratory airflow rates. A correlation between aerosol deposition and inspiratory flow rate was obtained in a study by Francis *et al* for a 4.5 µm MMAD aerosol (R^2>0.82 for nose added to nasal valve and, turbinates). The turbinate region was less affected by the increase in inspiratory airflow rate (+1% from 2-15 L/min) than the nose added to nasal valve (+5% from 2-15 L/min). An increase in maxillary sinus deposition was measured when the airflow rate increased (0.01% at 2 L/min to 0.09% at 15 L/min), but no correlation was obtained. Contrasting results were obtained by Leclerc *et al* with a nasal cast; using 0.55 µm and 2.8 µm aerosols with a 100Hz sound, they found that the amount of drug deposited in the maxillary sinuses increased when inspiratory flow rate decreased. The authors obtained 2-9 times more maxillary sinus deposition at 6 L/min than with standard inspiratory flow rate (sinus wave curve with a total of 15 L/min), demonstrating the influence of breathing patterns on drug deposition in anatomical regions of interest.

In conclusion, *in vitro* studies have demonstrated that an aerosol with an MMAD of 2-3 µm administered with the addition of a 100Hz sound, as performed by the NL11SN®, provides the optimal conditions for targeting the anatomical regions of interest for treating rhinology pathologies (maxillary sinuses, ethmoids and turbinates).

CLINICAL RESULTS

The positive impact of adding a 100Hz sound during radioactive gas (krypton) exchange between nasal fossa and maxillary sinuses has been demonstrated in healthy volunteers (see Figure 2B).[9,21] Vecellio *et al* found that 70% of the NL11SN® sonic aerosol was deposited in the nasal cavities of seven healthy volunteers, and 30% in the lungs; the pulmonary deposition resulted from the penetration of the small proportion of aerosol with a lower particle size. Study of radioactive deposition confirmed the homogeneous targeting of human nasal cavities, in particular the maxillary sinuses and ethmoid regions (respectively 0.5% and 1.1% of deposited aerosol).

Nasal corticotherapy has been evaluated recently for the treatment of olfactory disorders in chronic rhinosinusitis (CRS) patients with or without nasal polyps (respectively CRSwNP and CRSsNP). Reychler *et al* used the NL11SN® nebuliser to administer Pulmicort® (budesonide) in a sonic aerosol form and compared clinical results with those of Rhinocort® (budesonide) nasal spray and oral tablet Medrol® (prednisolone) therapy.[22] Treatment was conducted for 16 days, and the same dose of budesonide was administered to patients receiving nasal corticotherapy by spray or by sonic nebuliser. Clinical outcomes (Sniffin' sticks test, TDI scores) showed similar improvement of olfactory functions (OF) in patients receiving aerosol sonic treatment and oral treatment. No clinical benefit was observed for patients receiving the corticosteroid by nasal spray (Figure 4).

The clinical benefit for OF was the same for the two drugs administered at two different doses (32 mg of budesonide by sonic nebuliser *versus* 352 mg of oral methylprednisolone). This clinical response differed when the same drug was administered with the same dose via two different nasal devices (sonic nebuliser *versus* nasal spray).

The authors also found a significant difference in terms of nasal deposition of the budesonide depending on the nasal device used; the same dose of budesonide penetrated twice as far when administered by the NL11SN® than when it was administered by the nasal spray (*in vitro* study).

Reychler *et al* suggested that there is a relationship between the distribution of the deposited drug in the nasal cavities and the clinical effect observed in patients. A second study was performed on CRS patients with olfactory disorders. Goektas *et al* studied the OF (Sniffin' sticks test) of 15 CRS patients receiving oral prednisolone for 12 days (80 mg/day decreasing to 10 mg/day), and of 18 CRS patients receiving prednisolone by sonic aerosol for 12 days (total dose of 25 mg).[23] The authors also reported a significant OF improvement in all patients treated with oral prednisolone or by sonic aerosol ($p<0.05$). Both groups were equivalent for TDI scores after two months and after six months of follow-up.

Topical nasal administration with sonic nebulisers is also of clinical interest for antibiotic therapy. In particular, patients suffering from nasal polyposis (NP) often present recurring suppurations even after ethmoidal

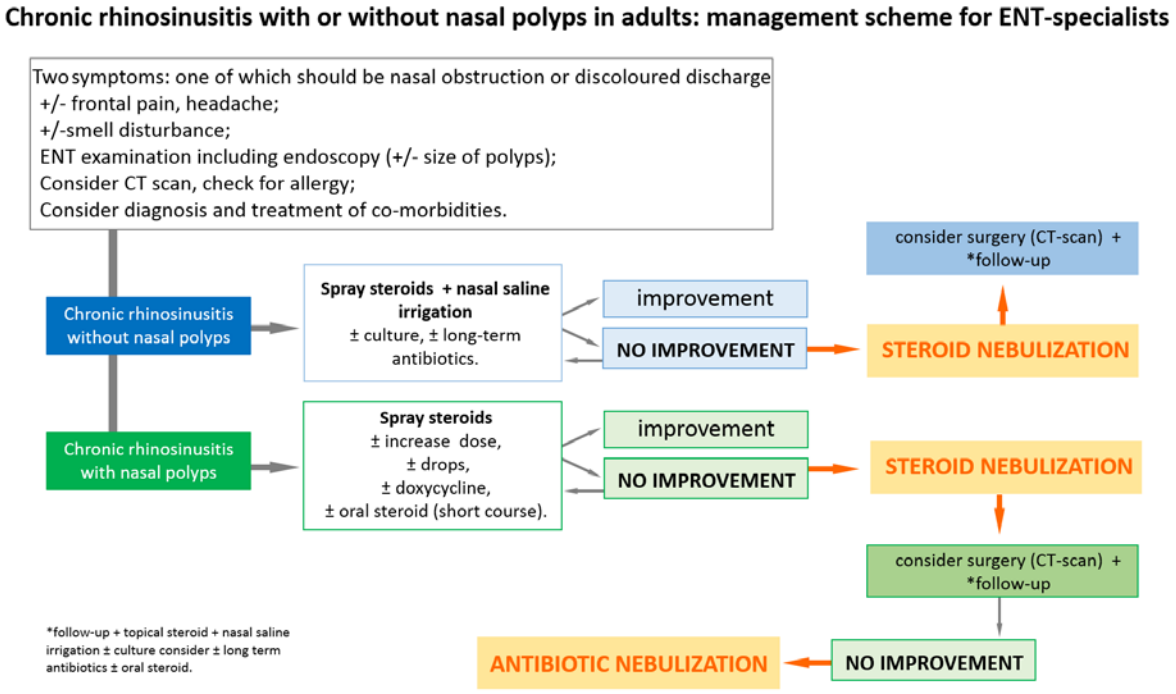


Figure 5: Proposal management scheme of chronic rhinosinusitis patients with and without nasal polyps for ENT specialist based on EPOS2012 scheme, including steroid and antibiotic sonic nebulisation. (Adapted from Fokkens et al.[4])

surgery. A preliminary study was conducted to determine the type of bacteria involved in these post-operative exacerbations (after radical ethmoidal surgery). Pathogenic bacteria isolated from 48 patients (80% of patients in the study) were predominantly identified as *Staphylococcus aureus* (60%) and Gram-negative bacteria. Nearly all the microorganisms were susceptible to antibiotics, including the aminoglycosides.[24] Based on this preliminary prospective study, tobramycin (150mg, Erempharma, Levallois-Perret, France) was selected for nasal nebulisation treatment in 72 post-operative NP patients (>2 months) who presented nasal suppurations (<3 months). After seven days of treatment, significant eradication of the bacteria was reported, compared with serum physiology treatment (respectively 46.9% and 17.4% of eradication; p=0.02).[25,26]

DISCUSSION

The prevalence of CRS in Europe is 10.9%, with marked geographical variation (range 6.9-27.1).[27] In the US, CRS affects 30 million people per year.

Corticosteroid sprays and nasal saline irrigations are recommended [4] for treating mild CRS, with additional oral antibiotics for moderate and severe cases. Surgery is considered when there is no improvement with these treatments. International recommendations do not include nebulisation to treat CRS.

Sonic nebulisation has been developed since 1981 and optimised to target anatomic regions to treat inflammation and infections in rhinology pathologies. The addition of a 100Hz sound and particles of 2-3 µm MMAD have been demonstrated to provide the optimal conditions for drug deposition in anatomical regions of interest including the maxillary sinuses. Sonic nasal nebulisation leads to deposition in the lung (70% in the nasal cavity and 30% in the lung), in the same way as nebulisers used in lung treatment produce deposition in the upper airways (30% in the upper airways and 70% in the lungs). This lung deposition could be a problem for future nasal drug development, with potential lung toxic effects. A new device named Easynose has been developed by DTF to allow fine particle administration via the nose without lung deposition and improving nasal and sinus deposition.[21]

Recent clinical studies [22,23,26] using the sonic nebuliser have demonstrated the efficacy of corticosteroids for olfactory functions and antibiotics for the eradication of nasal bacteria.

Comparison of sonic nebulisers and nasal sprays has shown that topical corticosteroid treatment is more effective with sonic nebulisation, demonstrating the possible interest of nebulisation when nasal spray treatment fails.

Comparison of sonic nebulisation and the oral route for corticosteroid administration has shown that similar clinical efficacy can be achieved by nebulisation with a lower dose, indicating that nebulisation could reduce side effects and be used to administer higher doses to improve clinical outcomes. These results support the interest of using sonic nebulisation for CRS patients, prior to (and after) sinus surgery.

Recently, a French consensus for nebulisation practices in rhinology [28,29] has been published, recommending the use of a sonic nasal nebuliser for the treatment of suppurative and oedematous rhinosinusitis, subacute rhinosinusitis (duration of symptoms 4-12 weeks), exacerbation of chronic rhinosinusitis and recurrent and suppurative post-operative rhinosinusitis (>1 month). This consensus, published by medical doctors, confirms the role of nasal nebulisation as a major tool for treating rhinology pathologies. Figure 5 proposes the inclusion of sonic nebulisation as a supplementary tool in the CRS-management scheme for ENT specialists.

Nasal nebulisation is of particular clinical interest for the treatment of rhinology pathologies and should be considered as an alternative and efficient drug administration route, in the same way as oral nebulisation is preferred under certain clinical conditions for lung treatment (compared with oral tablets, pMDI or DPI drug administration).

REFERENCES

1. *Van Cauwenberge P, Sys L, De Belder T, Watelet JB, "Anatomy and physiology of the nose and the paranasal sinuses". Immunol Allergy Clin North Am, 2004, Vol 24(1), pp 1-17.*
2. *Costantino HR, Illum L, Brandt G, Johnson PH, Quay SC "Intranasal delivery: physicochemical and thera-*

peutic aspects". Int J Pharm, 2007, Vol 337(1-2), pp 1-24.
3. Vidgren MT, Kublik H, "Nasal delivery systems and their effect on deposition and absorption". Adv Drug Deliv Rev, 1998, Vol 29(1-2), pp 157-177.
4. Fokkens WJ, Lund VJ, Mullol J, Bachert C, Alobid I, Baroody F, Cohen N, Cervin A, Douglas R, Gevaert P, Georgalas C, Goossens H, Harvey R, Hellings P, Hopkins C, Jones N, Joos G, Kalogjera L, Kern B, Kowalski M, Price D, Riechelmann H, Schlosser R, Senior B, Thomas M, Toskala E, Voegels R, Wang de Y, Wormald PJ, "EPOS 2012: European position paper on rhinosinusitis and nasal polyps". Rhinology, 2012, Vol 50(1), pp 1-12.
5. Laube BL, "Devices for aerosol delivery to treat sinusitis". J Aerosol Med, 2007, Vol 20(Suppl 1), pp S5-S17; discussion, pp S17-S18.
6. Suman JD, Laube BL, Dalby R, "Comparison of nasal deposition and clearance of aerosol generated by nebulizer and an aqueous spray pump". Pharm Res, 1999, Vol 16(10), pp 1648-1652.
7. Kundoor V, Dalby RN, "Assessment of nasal spray deposition pattern in a silicone human nose model using a color-based method". Pharm Res, 2010, Vol 27(1), pp 30-36.
8. Durand M, Rusch P, Granjon D, Chantrel G, Prades JM, Dubois F, Esteve D, Pouget JF, Martin C, "Preliminary study of the deposition of aerosol in the maxillary sinuses using a plastinated model". J Aerosol Med, 2001, Vol 14(1), pp 83-93.
9. Durand M, Le Guellec S, Pourchez J, Dubois F, Aubert G, Chantrel G, Vecellio L, Hupin C, De Gersem R, Reychler G, Pitance L, Diot P, Jamar F, "Sonic aerosol therapy to target maxillary sinuses". Eur Ann Otorhinolaryngol Head Neck Dis, 2012, Vol 129(5), pp 244-250.
10. Möller W, Schuschnig U, Celik G, Münzing W, Bartenstein P, Häussinger K, Kreyling WG, Knoch M, Canis M, Becker S, "Topical drug delivery in chronic rhinosinusitis patients before and after sinus surgery using pulsating aerosols". PLoS One, 2013, Vol 8(9), e74991.
11. Durand M, Pourchez J, Louis B, Pouget JF, Isabey D, Coste A, Prades JM, Rusch P, Cottier M, "Plastinated nasal model: a new concept of anatomically realistic cast". Rhinology, 2011, Vol 49(1), pp 30-36.
12. Möller W, Schuschnig U, Bartenstein P, Meyer G, Häussinger K, Schmid O, Becker S, "Drug delivery to paranasal sinuses using pulsating aerosols". J Aerosol Med Pulm Drug Deliv, 2014, Vol 27(4), pp 255-263.
13. Diot P, "NUAGES : Enquête national sur l'aérosolthérapie par Nébulisation, Usages et Avenir en médecine Générale Et Spécialisée". 2005, http://www.splf.org/s/spip.php?article215.
14. De Monte M, Scruignec J, Dubus JC, de Monte M, Scruignec, J, Dubus JC, Chaumuzeau JP, Dautzenberg B, Dessanges JF, Becquemin MH, Diot P, "N.U.A.G.E.S: a survey of nebulization practice in France with regard to ERS guidelines". Respir Med 2007, Vol 101(12), pp 2561-2565.
15. Guillerm R, Badre R, Flottes L, Riu R, Rey A, "Nouveau procédé assurant la pénétration des aerosols dans les sinus. [A new method of aerosol penetration into the sinuses.]". Presse Med, 1959, Vol 67, pp 1097-1098.
16. Durand M, Vecellio L, Aubert G, Chantrel G, Prades JM, "In vitro study of sonic aerosol to maxillary sinuses treatment". 2005, RDD Congress.
17. Francis M, Le Pennec D, Williams G, Duclos E, Diot P, Vecellio L, "In vitro study of aerosol deposition in nasal cavities during inhalation and exhalation". 2013, Drug Delivery to the Lung conference, Edinburgh.
18. Le Guellec S, Le Pennec D, Gatier S, Leclerc L, Cabrera M, Pourchez J, Diot P, Reychler G, Pitance L, Durand M, Jamar F, Vecellio L, "Validation of anatomical models to study aerosol deposition in human nasal cavities". Pharm Research, 2014, Vol 31(1), pp 228-237.
19. Leclerc L, Pourchez J, Aubert G, Leguellec S, Vecellio L, Cottier M, Durand M, "Impact of airborne particle size, acoustic airflow and breathing pattern on delivery of nebulized antibiotic into the maxillary sinuses using a realistic human nasal replica". Pharm Res, 2014, Vol 31(9), pp 2335-2343.
20. Leclerc L, Pourchez J, Prevot N, Vecellio L, Le Guellec S, Cottier M, Durand M, "Assessing sinus aerosol deposition: benefits of SPECT-CT imaging". Int J Pharm, 2014, Vol 462(1-2), pp 135-41.
21. Vecellio L, De Gersem R, Le Guellec S, Reychler G, Pitance L, Le Pennec D, Diot P, Chantrel G, Bonfils P, Jamar F, "Deposition of aerosols delivered by nasal route with jet and mesh nebulizers". Int J Pharm, 2011, Vol 407(1-2), pp 87-94.
22. Reychler G, Colbrant C, Huart C, Le Guellec S, Vecellio L, Liistro G, Rombaux P, "Effect of three-drug delivery modalities on olfactory function in chronic sinusitis". 2014, Sep 16, Laryngoscope.
23. Goektas O, Lau L, Olze H, "Treatment of chronic rhinosinusitis with pressure-pulsed corticosteroid inhalation". Indian J Otolaryngol Head Neck Surg, 2013, Vol 65(Suppl 2), pp 402-405.
24. Day N, Mainardi JL, Malinvaud D, Bonfils P, "Bacteriological study of ethmoid specimens from patients with nasal polyposis after ethmoidal surgery". Ann Otolaryngol Chir Cervicofac, 2009, Vol 126(4), pp 196-202. (doi: 10.1016/j.aorl.2009.06.004.)
25. Escabasse V, "Les indications en rhinology". Symposium Aérosolthérapie en rhinologie, Congrès SFORL 2014.
26. Bonfils et al, European Annals of Otorhinolaryngology, Head and Neck Diseases, in press.
27. Hastan D1, Fokkens WJ, Bachert C, Newson RB, Bislimovska J, Bockelbrink A, Bousquet PJ, Brozek G, Bruno A, Dahlén SE, Forsberg B, Gunnbjörnsdóttir M, Kasper L, Krämer U, Kowalski ML, Lange B, Lundbäck B, Salagean E, Todo-Bom A, Tomassen P, Toskala E, van Drunen CM, Bousquet J, Zuberbier T, Jarvis D, Burney P, "Chronic rhinosinusitis in Europe--an underestimated disease. A GA²LEN study." Allergy, 2011, Vol 66(9), pp 1216-1223. (doi: 10.1111/j.1398-9995.2011.02646.x. Epub 2011 May 24.)
28. Serrano E, Jankowski R, Le Taillandier de Gabory L, Stoll D, Crampette L, Gilain L, Escabasse V, zercodani J, Michel J. 2014. Consensus formalisé sur la nébulisation en rhinologie, Société Française d'Oto-rhino-laryngologie et Chirurgie de la Face et du Cou.
29. Serrano E, Le Taillandier de Gabory L, Vecellio L, Escabasse V, Crampette L, "Aerosoltherapie en rhinologie, guides des pratiques 2014". Symposium SFORL Congress 2014, Paris, France".

January 28-30, 2015
Boca Raton Resort & Club
Boca Raton, FL

19th Annual

DRUG DELIVERY PARTNERSHIPS™

Accelerating the Road to Market Success Through Innovative Partnerships

VISIONARY KEYNOTE

Bridging Science and Technology to the Healthcare of Tomorrow: Lessons Learned And New Paths to Explore

John Ludwig
SVP, BioTherapeutics Pharmaceutical Sciences,
Pfizer

SAVE $800 by Nov. 14! Use code **ODD**

Challenges and Success in Delivery of Biologics

Anand Subramony
Vice President, Drug Delivery & Device Development,
MedImmune

Pharmacogenomics and Personalized Medicine

Sven Stegemann
Professor for Patient Centric Product Design and Manufacturing,
Graz University of Technology, Austria

NEW for 2015!

- Regulatory Guidance for the $100 BN Combination Products Market
- Never before heard case studies from Sanofi, Janssen, Pfizer and more
- Delivering Effective Patient-Centric Therapeutics

Back by popular demand

partneringONE®
Jumpstart your next multi-million dollar deal

Register at **www.DDPEvent.com** | @DrugDeliveryIIR #DDP15

EFFECTS OF STATIC ON PLASTICS USED IN DRUG DELIVERY DEVICES

Drug delivery in dry-powder and aerosol inhalers can be hindered by static attraction of the drug substance to plastics used in the drug flow path. Here, Joel R Bell, PhD, International Technology Manager, and Josh Blackmore, MBA, Global Market Manager, Healthcare, both of RTP Company, report a series of projects to characterise this interaction, measure the effect of static build up and create new conductive plastic solutions to reduce the static charge in plastics used in the drug flow path of delivery devices.

INTRODUCTION

Dry-powder inhalers (DPIs) and pressurised metered-dose inhalers (pMDI) have been around for many decades. Both drug delivery technologies face some of the same challenges when compared to oral medication or injections. One of the key challenges for inhalers is effectively to measure the amount of drug that is dispensed *versus* the amount of drug that reaches the patient through their lungs. Drug formulations can stick in the drug packaging, the drug flow path, the back of the throat or tongue, and some may not reach deep enough in the lung to provide maximum effectiveness. Each variable is critical and must be accounted for and managed to improve consistent drug delivery.

This paper focuses on improving drug dosage accuracy by eliminating the static attraction between the drug formulation and the plastics used in the drug flow path of the device.

BACKGROUND ON STATIC ELECTRICITY

Everyone is familiar with static electricity and has experienced its effects from a young age. Simply rub a balloon on your head and watch as your hair stands on end as the balloon is slowly moved away. This happens because electrons from your hair are transferred to the balloon surface during rubbing (called tribocharging) and the difference in charge on the two surfaces causes attraction. Simply put, static electricity is the accumulation of charge (positive or negative) on a non-conducting surface.

Polymers (plastic) are inherently insulative and thus components made of plastic can easily accumulate charge on their surfaces. This charge can attract dust to the surface of the part; in medical drug delivery devices such as inhalers this surface attraction can cause particles of drug formulation (or other particles) to adhere to the surface resulting in reduced and inconsistent dosage. In more severe cases, an electrostatic discharge (ESD) event can take place when the charged surface comes in contact with a highly conductive object (ground) and the charge is rapidly released. Touching a metal doorknob and receiving a mild shock is a common everyday occurrence of ESD, but in certain situations ESD can damage or destroy sensitive electronic components, erase or alter magnetic media, or set off explosions or fires in flammable environments. Each year, many billions of dollars in losses due to ESD damage occur in the electronics industry alone.[1-2]

CONDUCTIVE STANDARDS, SPECIFICATIONS & TESTS

Three performance characteristics, surface resistance, resistivity, and static decay rate, are typically evaluated for conductive thermoplastic compounds. Surface resist-

Dr Joel R. Bell
International Technology Manager

Mr Josh Blackmore
Global Market Manager, Healthcare
T: +1 989 835 6493
F: +1 507 454 2041
E: jblackmore@rtpcompany.com

RTP Company
580 East Front Street
PO Box 5439
Winona
MN 55987-0439
United States

ance and static decay are directly measured, while volume or surface resistivity is derived from the measured surface resistance. There are standards in place to measure each of these properties and the measured values are only meaningful if the test procedures (equipment, geometry, environmental conditions, etc) are referenced.

Surface resistance is the ratio of direct current (DC) voltage to the current flowing between two electrodes and is expressed in ohms (measured value is dimensional). The US American Society for Testing and Materials' ASTM D257 and the UD Electrostatic Discharge Association's ESD STM 11.11 are the methods utilised in measuring surface resistance of plastic materials. There are several types of equipment that can be used to measure this property; typically RTP Company uses a Prostat PRS-801, operating at 100 Volts, equipped with a two-point probe, and all surface resistance values in this paper were obtained using this equipment.

Surface resistivity is the surface resistance measured between two electrodes that form opposite sides of a square and is independent of the size of the square or its dimensional units. Surface resistivity is typically measured using a Voyager meter or a guarded ring and the units are ohms/square.

Volume Resistivity is the ratio of DC voltage per unit thickness to amount of current per unit area passing through a material and the units are ohm-cm.

Static decay rate is a measure of a highly resistive material's ability to dissipate static charge under controlled conditions. FTMS 101C/4046.1 describes the protocol for static decay rate testing. In the test, a 3x5 inch (7.62x12.7 cm) plaque of the material is charged to 5,000 Volts and then the amount of time to dissipate 99% of the voltage is measured. According to the MIL PRF 81705D specification for antistatic materials used in packaging, the time measured must be less than two seconds.

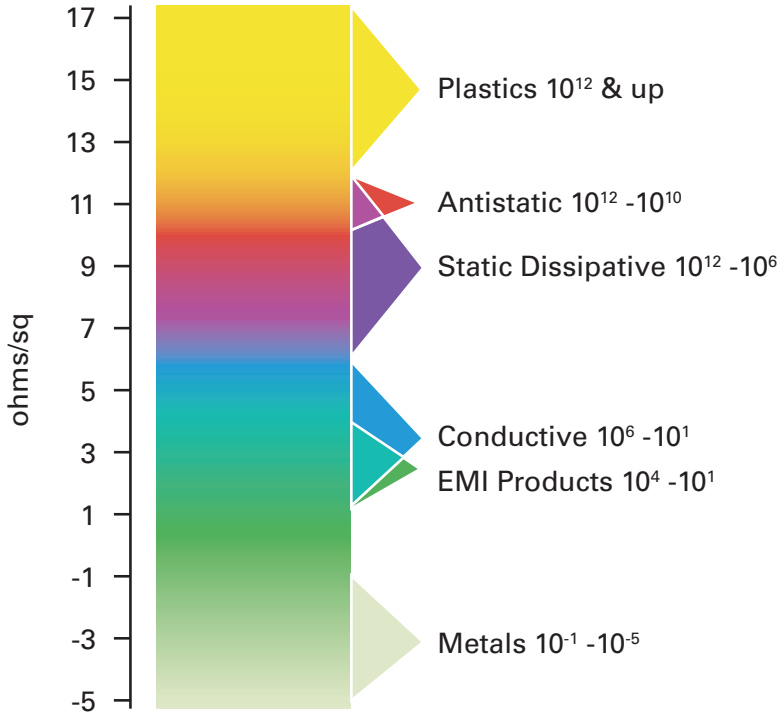


Figure 1: Surface resistivity spectrum for conductive materials.

CONDUCTIVE TECHNOLOGIES

Through the use of additive technologies, polymers can be made more or less conductive. Figure 1 shows a classification of materials based on their surface resistivity (inverse of conductivity). The type of additive technology will dictate the attainable level of conductivity, and Figure 2 shows the pros and cons for a selection of conductive technologies.

Conductive Technology	Pros	Cons
Migratory Antistats	• Economical • Non-permanent	• Process temperature limited
Inherently Dissipative Polymers (aka PermaStat®)	• Permanent • Transparent availability • Colourable • No loss of mechanical properties	• Limited to dissipative range • Process temperature limited
Carbon Black	• Economical • Dissipative or conductive • Resists tribocharging	• Sloughing • Black only • Lower impact strength
Carbon Fiber	• Dissipative or conductive • Reinforcing • Non-sloughing	• Anistropy • Poor triobcharging
Carbon Nanotubes	• Dissipative or conductive • Superior tribocharging performance • Minimal effect on mechanical properties and resin viscosity • Low LPC	• Cost • Black only
Metallic Additives	• EMI-FRI shielding • Highly conductive	• Limited colorability • Higher specific gravity

Figure 2: Table Summarising Conductive Technologies, and their pros and cons.

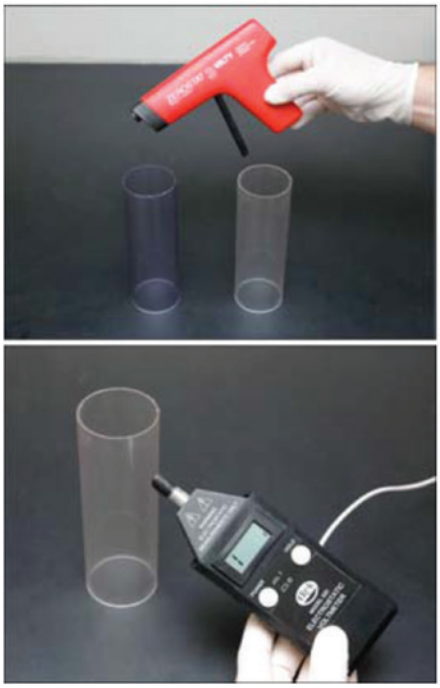


Figure 3: Top – tubes of the PermaStat® ABS (left-violet) and base ABS (right-clear) along with the Milty Antistatic Gun used to charge the tubes. Bottom – the voltmeter used to measure surface charge on a positively charged ABS tube.

Figure 4: Top – tubes of the PermaStat® ABS (left-violet) and ABS (right-clear) prior to testing. Bottom – powder retention in the two materials after testing.

As stated previously, plastics are inherently insulative and typically have surface resistivity values greater than 10^{12} ohm/sq. Antistatic compounds have surface resistivity values of 10^{10}-10^{12} ohm/sq and provide a relatively slow decay of static charge – from just hundredths of seconds to several seconds – thus preventing accumulations that may discharge or initiate other nearby electrical events. These compounds can be made one of two ways: by addition of a low-molecular-weight antistatic additive that migrates to the surface of the part, absorbs water, and then dissipates surface charge, or by the addition of an inherently dissipative polymer into the compound that forms a network structure with the base polymer. The first option is not permanent while the latter permanent option is the basis for RTP Company's PermaStat® antistatic technology.

Static dissipative compounds allow for dissipation or decay of static charges at a faster rate than anti-static materials (on the order of milliseconds) and are generally considered "optimal" for ESD protection. Compounds can be obtained using carbon particulate additives or by the addition of an inherently dissipative polymer.

Conductive compounds have surface resistivity values of 10^{1}-10^{6} ohm/sq and static decay rates on the order of nanoseconds. These compounds are achieved by addition of carbon fibre, high levels of carbon powder, carbon nanotubes, or other metallic additives. Performance is achieved by the charge being transferred through a percolated network of the conductive additive.

EXPERIMENTAL SETUP

A test was designed that simulated drugs coming into contact with the plastic walls in a drug delivery device, such as an inhaler. The effects static charge has on drugs sticking to the device were measured for antistatic and non-antistatic compounds. Materials were chosen to ensure that visual as well as quantitative comparisons could be measured.

MATERIALS

Acrylonitrile butadiene styrene (ABS) has good impact properties and is economical. It offers a good material for inhaler applications. In addition, PermaStat® ABS can be made transparent, which aids in visualisation. For the experiments presented here, RTP Company's clear PermaStat® ABS is compared with the base ABS resin.

Often, it is the interaction between the carrier material and the plastic component that needs to be controlled in DPIs. Lactose powder is a typical carrier material for the pharmaceuticals used in DPIs and therefore was used in this experiment. The specific lactose powder used was InhaLac® 230 (Meggle, Wasserburg, Germany).

"Often, it is the interaction between the carrier material and the plastic component that needs to be controlled in DPIs"

DEVICE DESIGN

A tube was used to simulate the chamber in a DPI. The dimensions for the tube were 2 inches (5.08 cm) diameter by 6 inches (15.24 cm) long, with a 1/16 inch (0.16 cm) thick wall. This geometry allowed for maximum surface area without unwanted interactions with part corners. The tubes were extruded by Thermoplastic Processes (Stirling, NJ, US).

TEST PROCEDURE

All tubes were cleaned and conditioned at 50% humidity prior to testing. For the test, each individual tube was weighed using an A&D Balance (FR-200 MKII, ± 0.0001g). A positive or negative charge was then placed on the tube using a Milty Zerostat [3] Antistatic Gun. The charge was confirmed using a Trek Electrostatic Voltmeter (Model 520) (Figure 3).

Lactose powder, 400 mg, was then inserted into the tube and then ends were sealed. The tube was continuously rotated to ensure the powder contacted the entire inside surface area of the tube. All free flowing lactose powder was then removed and the tube was reweighed. The powder retained in the tube was then calculated and percentage powder retention (weight of powder left in tube/initial weight of powder x 100%) was determined. A minimum of five tubes for each set of conditions (charge and plastic type) was measured for statistical accuracy.

RESULTS

Figure 4 shows the typical appearance of the tubes after testing. From the picture it is clear that there is more lactose powder stuck to the surface of the non-PermaStat® tube (clear tube). Quantitative results showed that <2.5% of the lactose powder was retained in the PermaStat® ABS tubes regardless of charge while >20% of the lactose powder stuck to the positively charged ABS tubes. The amount of powder that stuck to the negatively charged ABS tubes was reduced, but >8% was still retained. During testing, the surface charges on the tubes were monitored using the voltmeter and the PermaStat® tubes were able to dissipate the charge while a charge remained on the ABS tubes throughout the experiment. This inability to dissipate static surface charge caused the ABS tubes to perform less favourably.

Results from this experiment agree with previous experiments that show electrostatic charge affects drug delivery in inhaler type devices.[3-4]

Another key result is that the variability in the results for the ABS tubes is far greater than for the PermaStat® tubes. The standard deviation for the ABS tubes was ±8.9% for the positively charged tubes while it was only ±0.7% for the PermaStat® tubes. This could mean that drug delivery devices with less conductive surfaces in the drug flow path exhibit greater dose variability than those with more conductive surfaces, which will affect the ability of a drug delivery device to deliver consistent doses to a patient.

> "Results from this experiment agree with previous experiments that show electrostatic charge affects drug delivery in inhaler type devices"

CONCLUSIONS

Static charges that build up on the plastics used in the drug flow path and housing materials in pMDIs and DPIs have demonstrated the ability to attract the drug formulation and therefore potentially reduce the amount of drug delivered. A decrease in dose consistency is also a potential problem. Antistatic plastics would help to eliminate these effects in both pMDI and DPI devices.

REFERENCES

1. *Jonassen N, "Electrostatics", Chapman & Hall, New York, US, (1998).*
2. *RTP Company Conductive Specialty Compounds Brochure.*
3. *Peart J, Kulphaisal P, Orban JC, "Relevance of Electrostatics in Respiratory Drug Delivery". Business Briefing: Pharmagenerics, 2003.*
4. *Wildhaber JH, et al, "Electrostatic charge on a plastic spacer device influences the delivery of salbutamol". Eur Respir J, 1996, Vol 9, pp 1943-1946.*

We put no limits on curiosity

Imagination and curiosity are the starting points for 3M innovation – the kind of curiosity that leads to innovative solutions for real world problems – such as creating the first metered dose inhaler, enabling patient-centric transdermal technology and converting microreplication technology to microneedle delivery systems. From development, to scale up and commercialization, let the curious minds at 3M Drug Delivery Systems provide innovative solutions to your drug delivery challenges.

Curious? Scan an icon to learn more*

or go to 3M.com/DDS

layar
Download the free Layar app

*Scan each icon to unlock more about each technology.

3M DRUG DELIVERY SYSTEMS

3M