

PULMONARY & NASAL DRUG DELIVERY

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- Jan: Ophthalmic Drug Delivery
Feb: Prefilled Syringes
Mar: Transdermal Patches, Microneedles & Needle-Free Injectors
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June: Injectable Drug Delivery: Pharmaceuticals Focus
July: Novel Oral Delivery Systems
Sep: Drug Formulation & Delivery Solutions & Services
Oct: Prefilled Syringes
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Front cover image 'MDI valves on a filling line' supplied by Coster, whose article appears in this issue, page 21. Reproduced with kind permission.

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ONdrugDelivery **2014** EDITORIAL CALENDAR

Publication Month	Issue Topic	Materials Deadline
January	Ophthalmic Drug Delivery	December 9th
February	Prefilled Syringes	January 13th
March	Transdermal Patches, Microneedles & Needle-Free Injection	February 10th
April	Pulmonary & Nasal Drug Delivery	March 10th
May	Injectable Drug Delivery: Devices Focus	April 14th
June	Injectable Drug Delivery: Pharmaceuticals Focus	May 12th
July	Novel Oral Delivery Systems	June 9th
September	Drug Formulation & Delivery, Services & Solutions	August 4th
October	Prefilled Syringes	September 15th
November	Pulmonary & Nasal Drug Delivery (OINDP)	October 13th
December	Delivering Biotherapeutics	November 10th



PRODUCT DIFFERENTIATION IN AN EVER-SHIFTING INHALATION LANDSCAPE

In this insightful overview piece, Richard Beesley, Inhalation Drug Delivery Business Manager at 3M Drug Delivery Systems, discusses how the pharma industry has changed over the years and how these changes impact today's industry (in particular the pulmonary and nasal delivery device industry). Richard also examines how current global factors from both within and outside the pharma industry, such as increasing patient awareness and the current regulatory focus on compliance and human factors, can affect business. In addition, he addresses how recent innovations from 3M, including the 3M™ Integrated Dose by Dose Counter and the 3M™ Nasal MDI, can be used to meet the needs of today's market.

Since the invention of the pressurised metered-dose inhaler (MDI) approximately 60 years ago, the industry has undergone constant evolution. If we think back over the events and global changes in just the past 30 years, it becomes clear how difficult it is to forecast what lies ahead. Thirty years ago, in the mid-1980s, compact discs were just being introduced and the Cold War was an ongoing concern. As we know, the pharmaceutical and drug delivery markets were very different then too, a testament to the furious pace of change in the past several decades. The industry has undergone an evolution on many basic levels,

"AS VETERANS OF THIS BUSINESS KNOW, THERE IS NO "TYPICAL" LIFECYCLE FOR AN INHALATION PRODUCT"

with players adapting to compete, be first to market, cope with changes in raw materials and formulations, and meet new regulations. As environmental concerns rose, The Montreal Protocol led to the phase-out of chlorofluorocarbons (CFCs), which changed the inhalation industry dramatically.

Today, we see the evidence of that successful adaptation. Both MDIs and dry-powder inhalers (DPIs) combine to form a market valued at US\$37 billion (£23 billion) annually.¹ Of the 920 million devices sold each year, MDIs represent about 60% of the volume and 40% of the sales value.² MDIs are primarily used to treat chronic obstructive pulmonary disease (COPD) and asthma, although they can be used to also treat a wide range of other therapeutic areas. In fact, we are now seeing a resurgence of nasal MDIs for allergies.

While the MDI market moves forward, patient compliance is growing in focus, highlighting one likely trend for the future. An estimated \$290 billion in additional costs is spent annually due to non-compliance, and estimates show the industry loses approximately \$188 billion in profits due to this issue.³ These "human factors" have become more of a concern for the US FDA, which is leading to greater regulations around the issue.

Beyond the increasing focus on compliance, financial pressures have also acted on the industry. A growing number of mergers and acquisitions has significantly consolidated the industry players and resulted in moves to and from outsourcing, and back again. Blockbusters have lost



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patent protection and faced new generic competition. Pressures like these have forced the industry to be faster and leaner. Almost none of these factors could have been accurately predicted 30 years ago, and similarly, we do not know now what will come in the next decades. The only thing that players in the pharmaceutical industry can do is proactively manage their businesses to be ready for change, and ideally drive that change.

DRIVING INNOVATION IN A CHANGING WORLD

As veterans of this business know, there is no “typical” lifecycle for an inhalation product. A seemingly robust product’s lifespan can be quickly reduced by new developments or generic competition. If we consider how drugs are developed, we see that the first step—the research phase for chemical targets to address particular therapeutic areas—can take anywhere from one to three years, and sometimes more. Once this phase is complete, the process moves on to development, when the drug goes through testing to determine its safety, efficacy, and a range of other attributes in order to prepare it for regulatory submission and approval. This phase can add seven to 10 more years to the timeline. Finally, the product is ready to hit the market. At this point, companies can expect 6-10 years of patent protection before generics are introduced. The product can then stay on the market—albeit in a more competitive environment—for any period of time.

It is at this stage that differentiation becomes key for a product’s success, protecting it from generic competition. To achieve this, pharmaceutical companies and their partners must devote significant time and resources to research and development. 3M Drug Delivery Systems has seen this strategy pay off successfully with the introduction of dose counters. The 3M™ Integrated Dose by Dose Counter was developed to help improve compliance and to give patients a reliable and easy-to-use tool that builds their confidence in their MDI (see Figure 1). The dose counter has a displacement-driven design that eliminates under-counting, while the split-count principle avoids over-counting. With a familiar look and clear display, it requires no additional training for patients, and its ergonomic design suits a wide range of users.

This technology was developed specifically with patients in mind, with significant research devoted to understanding the features that are most important to users of the device. Testing has shown that the dose counter not only meets patients’ expectations, but actually enhances their experience of using an MDI. This technology is the first integrated dose counter with FDA approval available to third parties.



Figure 1: The 3M™ Integrated Dose by Dose Counter has a familiar look and clear display, and requires no additional training for patients.

DIFFERENTIATING TO MEET PATIENTS’ NEEDS

An innovation like the dose counter can be a big help to a company looking to differentiate its product in the marketplace and drive patient preference (Figure 2). Today’s patients are increasingly looking for simpler ways to administer medication to fit with their busy

“THE MOBILE TELECOMMUNICATIONS INDUSTRY IS IN A CONSTANT COMPETITION TO ENHANCE DEVICE INTERFACES – A COMPETITION DRIVEN BY INCREASED AWARENESS AND CONSIDERATION OF HOW CUSTOMERS INTERACT WITH PRODUCTS. THE WORLD OF DRUG DELIVERY IS NO DIFFERENT, AND THE SAME LEVEL OF INNOVATION IS NEEDED”

schedules. We need look no further than the growing number of smartphone apps and other tools patients use to monitor their health intelligently in order to see that they expect, and want, to be more informed about their treatments. Given this trend, it is not surprising that patients state that they value having an accurate dose counter on their inhalation device, and that it ranks as one of their favourite features.



Figure 2: The technology was developed specifically with ease of use and patient preference in mind. Testing has shown the dose counter enhances the patient’s experience of using an MDI.

“WE NEED LOOK NO FURTHER THAN THE GROWING NUMBER OF SMARTPHONE APPS AND OTHER TOOLS PATIENTS USE TO MONITOR THEIR HEALTH INTELLIGENTLY IN ORDER TO SEE THAT THEY EXPECT, AND WANT, TO BE MORE INFORMED ABOUT THEIR TREATMENTS”

As noted previously, there is a strong drive in the pharmaceutical industry towards taking human factors into account to promote patient compliance. To do this, a business must not only consider the therapeutic needs of patients, but also the needs they develop from using other products in their day-to-day lives. For example, the mobile telecommunications industry is in a constant competition to enhance device interfaces – a competition driven by increased awareness and consideration of how customers interact with products. The world of drug delivery is no different, and the same level of innovation is needed. At 3M, patients are surveyed on every aspect of an inhalation device at the prototype level to help developers ensure that new technologies will be patient-approved and patient-preferred. Nearly any change to a 3M device is directed or strongly influenced by patient feedback.

Of course, any innovation that gains attention and preference from patients will likely eventually be mimicked by competitors. This fact is not unique to the pharma industry. In reality, companies simply must invest in new research and development on an ongoing basis; it's the cost of doing business today.

At 3M, this is evidenced by a new nasal MDI device, which is driving real change in the nasal inhalation market. Again, the development of this product was strongly driven by research into patients' wants and needs. Data showed that patients found aqueous pump sprays for allergic rhinitis to be unpleasant in both sensation and taste, as well as unhygienic.⁴ The new 3M™ Nasal MDI, however, is designed with a no-drip spray designed to eliminate nasal run-off and post-nasal drip, and to minimise aftertaste. It also has a twist-and-lock design that is simple, compact and patient-approved. A technology such as this can make an ideal route for pharmaceutical companies seeking a rapid extension of their inhaled corticosteroid into allergic rhinitis, or for those seeking a device edge for new nasal treatments.

COPING WITH REGULATION

Even when a pharmaceutical company is doing everything it can to drive innovation and proactively manage product lifecycles, there are still many challenges from outside forces to keep in mind. The tighter regulatory require-

ments of the US are becoming more common around the world, as emerging markets use US and EU regulations as their benchmarks. This trend not only increases the standards, but ultimately the cost to enter these markets.

Furthermore, legislation surrounding good manufacturing practices (GMP) for pharmaceutical companies has been put in place in many countries, which enhances the final quality of the product. It also improves working conditions within pharma and drug delivery manufacturing, a welcome development. Many companies in the industry already have high internal standards in place. For instance, 3M utilises Lean Six Sigma manufacturing and process controls to ensure the quality of products. Increasing legislation in this area helps ensure that everyone considers these factors.

Regulations also come into play as more blockbuster patents have come close to expiry or expired. In these cases, regulators must determine how to manage and control new generic copies of these products. Currently, bio-equivalency of the generic copy is the focus of regulations, which is driving technologies that can replicate existing products while navigating the extremely complex patent landscape. Testing of these products centres on comparing the new generic with the innovator in order to confirm that it fits within the existing approved product specification. All of these regulatory developments work as a constant driver of change as companies attempt to stay ahead of both legislation and the competition.

THE IMPACT OF THE OUTSIDE WORLD

Material substitution is also presenting distinct challenges. Even a seemingly simple material substitution can have a major impact on a product. The pharma industry uses many materials in a low volume compared with other industries, so it can sometimes be significantly impacted by changes driven from the outside. For example, we use polymers in sealing rings, and these same polymers are used in high volumes in other industries. If another industry requires a design change or switches to an alternative product, the pharmaceutical community can be impacted. The cost of the polymer can increase dramatically, or we may even have to

re-qualify the new variation of polymer to ensure it still complies with regulations. In some cases, both of these changes can occur, with the manufacturer being impacted by both increased cost and re-qualification. Considering the broad range of components that the inhalation industry uses across the 920 million devices produced each year, combined with heavy regulatory requirements, the situation is a recipe for continual change.

Given these constant changes, many companies in the pharmaceutical industry look to outsource or in-source at various stages in the value chain. For instance, a company may buy late-stage drug developments that it can then commercialise directly or with a partner. By doing this, the company can scale-back its upfront investment. Additionally, the practice of outsourcing commercial manufacturing of products is growing. While companies initially were outsourcing to emerging markets in order to reduce costs, today we are seeing more use of specialist contract manufacturing organisations in the EU and US. By working with these manufacturers, a pharmaceutical company can gain added value in the total lifecycle of its product.

FINDING THE RIGHT PARTNER

Any investment or partnering model must of course be aligned with a larger strategic intent, but outsourcing of manufacturing is often attractive to companies which do not want to make the capital investment in equipment and infrastructure that is required to manufacture inhaled products. However, in order to optimise a product's chances of success and extend its lifecycle, it is vital to pick the right partner—one that has stability, experience, and the advanced knowledge required truly to add value.

With more than 50 years of global MDI manufacturing experience, 3M Drug Delivery Systems has worked with many pharmaceutical companies to help differentiate their products and position them for a long life. With a proven track record of innovation and swift adaptation to new challenges, 3M has provided its problem-solving expertise and forward-thinking skills to numerous partners. With recent innovations like the 3M Integrated Dose by Dose Counter and the 3M Nasal MDI, 3M has demonstrated its unmatched capabilities in responding to patients' needs, regulatory demands, and the constant drive for product differentiation.

REFERENCES

1. *3M market assessment.*
2. *IMS 2012.*
3. *Pharmaceutical Executive, June 2013.*
4. *3M commissioned market research, December 2009, USA & UK, n=64.*



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COMPANY PROFILE TEAMTECHNIK GROUP

HIGH VOLUME PRODUCTION: DRUG DELIVERY DEVICES ON THEIR PATH TO SUCCESS



With its modular TEAMED platform system, teamtechnik Group offers a scalable production solution for assembly and test of drug delivery devices.

PHASE I TRIALS: PROTOTYPE PRODUCTION WITH TEAMED POP

Normally customers approach teamtechnik with their device still under development. In such cases teamtechnik offers the TEAMED PoP (proof of principle) machine and the possibility to perform and to monitor the critical processes with fully-automatic solutions at a very early stage (Figure 1).



Figure 1: TEAMED PoP robot station.



Figure 2: TEAMED Stand-alone: refined process automation.

PHASE III: SMALL VOLUME PRODUCTION WITH TEAMED STAND-ALONE

The same process units are integrated into the TEAMED Stand-Alone machine: a semi-automatic assembly line (Figure 2). Almost all assembly operations are performed by -automatic stations, the refined process stations are still the same as in the TEAMED proof of principle machine.



Figure 3: TEAMED fully automatic high-volume line.

MARKET SUCCESS: HIGH VOLUMES WITH TEAMED

For a high-volume output machine running 24/7, teamtechnik offers the TEAMED fully-automatic high-volume line (see Figure 3). All parts are delivered by bowl feeders or palletising systems. Carrier design is again identical to the proof of principle machine and the processes have also been already validated at the TEAMED PoP. These benefits are achieved only with the very strong modular design (Figure 4) of the TEAMED platform, with individually replaceable processes.

Based in Freiberg, Germany, teamtechnik Group has been making intelligent and reliable automation solutions for medical and pharmaceutical and other industries. With a total of 800 employees teamtechnik Group has production sites in Germany, Poland, China and the US, and has a global service network.



Figure 4: The modular nature of the TEAMED system means it can be applied at a) proof-of-principle/Phase I, b) at small volume production levels/Phase III, and c) and at full high volumes for market production.

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MULTISENSORY TRAINING AND SMART DEVICES FOR IMPROVING PULMONARY DRUG DELIVERY

In this article, Craig Baker, Executive Vice-President, Noble, highlights the importance of device training in the effective treatment of diseases for which inhaler-delivered therapeutics are prescribed. He outlines recent advances in training techniques and the emergence of smart devices with training and error reporting functionality built in.

INTRODUCTION

A number of advantages exist with pulmonary administration for the treatment of chronic and acute conditions, that offer promising future growth in these markets. According to the US National Institutes of Health (NIH), a nominal dose is defined as “the total prescribed dose” of an inhalable therapeutic. Commonly observed actual doses (medicament effectively reaching the lung) however, are in the range 6-60% of the nominal dose. Such incomplete doses pose safety risks to patients and reduce the effectiveness of their treatments.

“THE RESULT IS AN EFFICIENT LEARNING EXPERIENCE FOR PATIENTS, WHICH BUILDS CONFIDENCE WITH A DEVICE WHILE IMPROVING ADHERENCE AND SAFETY”

Successful use of respiratory delivery devices depends on a number of factors including the properties of the lung, disease state, breathing patterns and delivery techniques. Using a respiratory drug delivery device can create anxiety for patients and leave them questioning their ability to self-administer. In order to prevent such outcomes, the industry has turned to education to support and empower patients.

A recent example of this education is the creation of a smart training device with sensor technologies and auditory instructions that measure the flow rate and velocity of inhalations and provide feedback to patients in real-time. The result is an efficient learning experience for patients, which builds confidence with a device while improving adherence and safety.

Inhaled drugs have long been the preferred delivery route for respiratory-related indications, including asthma, COPD and cystic fibrosis. These conditions are characterised by inflammation, constriction or obstruction of airways and the lung. Such factors can adversely affect the

functions of the lung and are best treated with targeted therapies such as anticholinergics, beta-agonists or corticosteroids. The efficiencies of targeted therapies that treat these conditions lie in the localisation and rapid uptake in the lungs.

In recent years, the absorption of drugs for systemic delivery has become an attractive

option to treat a number of chronic conditions with the delivery of antibodies and therapeutic proteins. As these therapeutic categories continue to grow, more patients and healthcare professionals (HCPs) will find themselves interfacing with and learning how to use respiratory drug delivery devices. A strong foundation and learning experience from day one is the first step in promoting healthy outcomes and adherence



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for patients. As a result, innovative educational products with smart technologies are changing the way brands educate patients throughout the product lifecycle, from product launches to the revitalisation of established brands.

PULMONARY DRUG DELIVERY

The ventilatory or respiratory system consists of several major components that enable the breathing processes. As we inhale, the diaphragm and inspiratory muscles contract, drawing air through the nasal/oral cavity and through airways until it reaches the alveoli sacs of the inner lung. Within the alveoli, oxygen passively diffuses across the capillary endothelium and into the bloodstream, where red blood cells carry oxygen throughout the body until it is exhaled, mainly in the form of carbon dioxide.

By definition, autonomous patients are those able consistently and effectively to administer themselves a prescribed dose free of error. In order to reach this level, patients progress through a number of learning stages where motor and muscle skills are acquired and confidence is built. We call the early stages of this learning process “onboarding”, and it is characterised by highly variable outcomes. Errors experienced during the onboarding phase are gross and frequent in nature and are often avoidable through education and training programs. The use of smart and sensor technologies monitors patient behaviours and provides corrective feedback when a step is out of sequence or inhalation performance is insufficient. Such an approach provides patients the support needed to learn about their drug delivery device efficiently and autonomously manage their treatments.

Many of the variables effecting the nominal dose and disposition of drug molecules within the lung are dependent on a patient’s interaction with the device interface, specifically the force and timing of inspiratory efforts. These variables are determined by a drug’s physical properties such as mass/particle size and associated to optimal ranges of force and volume. Forces outside (+/-) this range adversely affect the disposition of the dose, reducing the absorption and therapeutic effect of the particles.

The table shown in Figure 1 serves as an evaluation of common steps associated with the delivery and effectiveness of an inhaled drug therapy. The severity and probability of harm are approximations based on observational studies of metered-dose inhalers (MDIs) and dry-powder inhalers (DPIs). A number of risk management strategies can mitigate these risks and preventable errors. Educating patients on techniques and behaviours associated with drug delivery devices is often a cornerstone of such strategies.

Step	Description	Risk of error
1	Prepare device	Low
2	Remove mouthpiece	Low
3	Inspect the mouth piece for obstructions	High
4	Prepare dose	Medium
6	Breath out, away from the device	High
7	Place device in mouth	Medium
8	Actuate dose	High
9	Inhale with the appropriate force and duration	High
10	Hold breath (as specified in IFU)	Medium
11	Repeat dose as prescribed	Medium
12	Clean and store device as prescribed	Medium

Figure 1: Table of Common Steps for Using Respiratory Delivery Devices.

METERED-DOSE INHALERS

Pressurised metered dose inhalers (pMDI) were first introduced in the 1950s. Today’s devices use many of the same scientific and behavioural properties as their predicates. These devices generally consist of a drug-containing canister, actuation mechanism, (external housing), metering valve, actuation nozzle and mouthpiece. When pressure is applied to the inverted canister, the metering valve is depressed, releasing a high-velocity spray that passes through the actuator nozzle and is expelled through the mouthpiece. The design and engineering of the actuation nozzle and expansion chamber determines the initial velocity, volume and orientation of the metered dose. Pressurised canisters house the active pharmaceutical ingredients and HFA propellants. The internal lining of these containers is often coated to prevent the adhesion of drug particles and increase the stability of the formulation over time. A second class of MDI’s, breath-activated metered-dose inhalers, are actuated by a patient’s inspiratory effort rather than depressing the canister.

DRY-POWDER INHALERS

An alternative to MDI’s are dry-powder inhalers (DPIs), which have experienced a steady rise in adoption in recent years. Often, a capsule containing a single dose in powder form is punctured and the powder is inhaled through the inhaler device. Active pharmaceutical ingredients are often contained in carrier particles that deliver the medicament to the appropriate region of the lung for absorption. Several environmental factors affect the performance of DPIs, including ambient humidity, which can adversely affect the flow and velocity needed to deliver the dose. Although there is no need to co-ordinate actuation with inhalation as is the case with MDIs, proper education and training is required to use and maintain DPI inhalers appropriately.

THE PATIENT EXPERIENCE

Scientific and technological advances have enabled much of the growth and success of the pulmonary delivery market. Companies are now focusing their attention on improving the patient experience within this delivery market. This requires a patient-centric approach to drug delivery, which begins with understanding the stages patients pass through during their treatment. This begins from the initial diagnosis and extends throughout the course of a patient’s treatment. The emotions experienced during these processes are unique to each stage and often require specific educational approaches to fully address. In addition to emotional stressors, a number of human factors must also be considered when applying a patient-centric approach. Following is a brief summary of both:

1. Psychological and emotional impact of diagnosis
2. Physical impairments associated with age and conditions
3. Fear and anxiety associated with self-administration, often leading to avoidance behaviours
4. Social needs of the patient, including family and medical support systems
5. Lack of experience and education with drug delivery devices leading to onboarding challenges
6. Synchronisation and muscle memory needed to safely and effectively administer with a pulmonary drug delivery device.

According to Dr Sam Pejham, Assistant Clinical Professor at the University of California, San Francisco, and creator of the smartphone app, AsthmaMD, easy access to the educational information is the first step in promoting patient adherence with respiratory inhalers. This often includes the development of therapeutic action plans to help patients identify

“DEVICE-TRAINING SOLUTIONS INCORPORATING MULTISENSORY TECHNOLOGIES, SUCH AS AUDIO, VISUAL, AND TACTILE FEEDBACK HAVE BEEN PROVEN TO STRENGTHEN NEUROLOGICAL CONNECTIVITY”

changes in their conditions and modify their therapies as required.

A recent study conducted by the NIH indicated that the majority of asthmatics do not adhere to their prescribed control inhalers but rather rely on their emergency inhaler for acute onsets. Through education and action plans, these types of events can be mitigated and adherence improved. As mentioned by Dr Pejham, priming, cleaning and inhaling with respiratory devices are problematic tasks for patients and often vary across drug manufacturers and devices. As a result, many physicians are hesitant in changing a patient's treatment after they have successfully on-boarded and established muscle memory to a specific device. Based on his experience, many patients do not have the ability to detect errors in their treatment, such as clogs in expansions chambers, which adversely affect the delivery of a full dose. Providing education and training

information to patients that help them adhere to their prescribed treatments and fulfil the functional requirements of devices is an effective strategy to improve patient outcomes and build brand loyalty with patients and health-care providers.

Understanding the needs of patient populations is the first step in effectively educating them. This often begins with condition and age-related impairments and ends with delivering a superior training experience. Modern neurological research suggests that information perception, encoding, decoding and retrieval is influenced by the strength and uniqueness of educational stimuli. Thus, device-training solutions incorporating multisensory technologies, such as audio, visual, and tactile feedback have been proven to strengthen neurological connectivity between semantic networks of the brain, a principle referred to as cross-modal processing. As a result, the effectiveness

of multisensory training devices is clinically superior to traditional means of education and complimentary to the objectives of brands, manufacturers and providers.

Due to the success of multisensory device training, smart technologies are now augmenting the training device market. Smart technologies provide the opportunity for brands to turn simulation devices into teaching devices that incorporate real-time error detection, notification and correction. This direct feedback process accelerates the learning process and becomes the most accurate, consistent and accelerated process when on-boarding patients to a drug delivery device.

At its core, the ultimate goal of device training is to create value for industry stakeholders by enhancing the patient experience, reducing the burden on HCPs and improving safety. As new brands continue to launch and augment markets, brands will continue looking for strategies to differentiate themselves from competitors. In the modern era of patient-centric care, those able to provide a superior product and educational experience to patients will be competitively positioned and benefit from the loyalty established by patients and HCPs.

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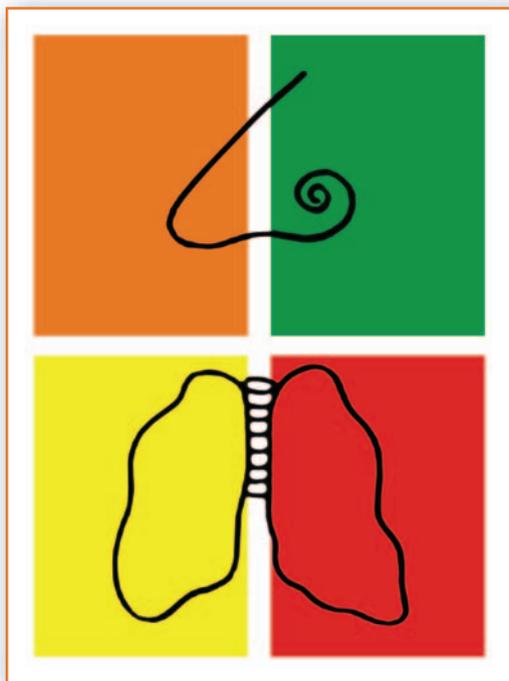
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CYCLOMIX FOR BLENDING DPI FORMULATIONS



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Blending formulations for dry-powder inhalers (DPIs) is a delicate matter. In order to disperse the actives in the lactose one needs to break up the cohesive forces between the fine particles, which requires a certain level of mechanical energy. If however the energy applied to the formulation is too high, then the adhesive forces between the carrier and the actives will be too high, which limits the separation during inhalation. Finding the right balance for the required mixing energy is the critical issue and calls for a very efficient mixer. Delivering a fully homogeneous blend, without deterioration of the particles is a prerequisite.

The Cyclomix (shown in Figure 1) proved to be perfectly suitable for this application.

In the mixer a combination of impact mixing and shear mixing is used. In the blender the product is rotated by an agitator with paddles and a knife blade. The rotational movement will apply centrifugal forces on the powder particles. This force will move the particles upwards along the wall of the conical vessel. At the top of the cone, the special-



- Blending process controlled by only mixing time and speed for a certain fill level
- Flexible fill level between 30-100%.

The Cyclomix is available in sizes ranging from 100 ml upwards (fully customised) and will support R&D in the various stages as well as production requirements.

ABOUT HOSOKAWA MICRON

Hosokawa Micron is a global industrial process machinery supplier which provides mixing, drying and agglomeration equipment and complete systems for the pharma industry.

Interested in the Cyclomix or any other Hosokawa powder processing technologies? Meet us at the DDL 24 conference in Edinburgh, stand 41.

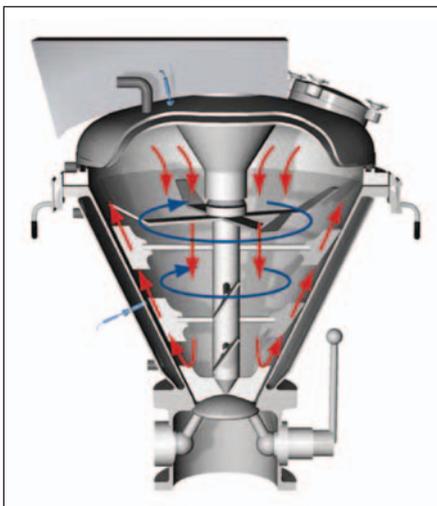


Figure 2: Schematic showing flow pattern inside the Cyclomix vessel.

Figure 1: Possible configuration of a 5 L Cyclomix machine.

ly formed dome will guide the particles downwards again through the centre of the vessel. This flow-pattern is combined with a rotational pattern indicated in Figure 2.

Further benefits of the Cyclomix design include:

- Central bottom outlet and the conical shape of the vessel result in a complete discharge, assisted by a slow rotation of the agitator if necessary
- Top-driven agitator without seals and bearings in the product zone. Various seal configurations are possible
- Various options for contained charging and discharging possible

“IN THE MIXER
A COMBINATION OF
IMPACT MIXING AND
SHEAR MIXING IS USED”

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e-DEVICE PLATFORMS: FROM HIGH-PERFORMANCE DRUG DELIVERY DEVICES TO SMART DEVICES FOR IMPROVING PATIENT COMPLIANCE

In this article, Aptar Pharma describes its latest innovation, e-Device platforms, which have recently been launched. The two new electronic devices, e-Dose Counter and e-Lockout, embrace current rapid increased acceptance of electronic devices in everyday life and are designed to take advantage of the benefits electronics can bring to the drug delivery device field in order to promote increased adherence and compliance.

Based on a presentation by Joachim Koerner, Vice-President e-Device platform R&D, Aptar Pharma Prescription Division.

Many patients with chronic diseases do not take their drugs as prescribed by their physician. Poor adherence to the prescribed regimen may cost as much as US\$300 billion (£186 billion) per year to the US healthcare system alone (Medco Studies).

Increasing the effectiveness of adherence interventions may have a far greater impact on the health of the population than any improvement in specific medical treatments (WHO, 2003). Additionally, studies from Health Maintenance Organisations (HMOs) are showing that improved patient compliance could lower healthcare management costs.

With the objective in mind of enhancing patient adherence, Aptar Pharma has been working since more than a decade ago on smart solutions leveraging electronics for future drug delivery devices.

REGULATORY DRIVERS

There is a growing trend by health authorities across the world towards increasing device regulations. For example, any new drug product using an asthma pressurised Metered Dose Inhaler in the US now needs to be fitted with a dose indicating or counting system to allow the patient to monitor the number of doses remaining. Another move applies to the regulation of multidose nasal spraying devices for controlled substances such as opioids that are

used to treat breakthrough pain. Some countries now require these devices to have a dose counter and/or a locking mechanism to prevent overdose and drug abuse.

Electronics offer the most attractive way forward. In the context of dose counters, electronic systems provide advantages; for example, allowing the device to display large and highly legible digits (compared with mechanical counters). Effective time-controlled robust locking systems can only be achieved with electromechanical components and so electronics are essential here.

MARKET ACCEPTANCE

User studies confirm that electronic drug delivery devices are now as well accepted by the majority of consumers as smart portable devices such as phones, games, and pads. Because these drug delivery devices are designed with a patient-centric approach, the targeted patient population finds them very convenient to use. Furthermore, electronics are getting smarter, requiring less power consumption, having a higher integration level, and incorporating more functionality. In our daily lives, electronics are becoming increasingly visible.

Ease of use is key to the design of a successful electronic device. For example, there must be no need to replace the batteries; the user doesn't want to get involved with tasks such as this.

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TWO NOVEL SMART DELIVERY DEVICES FOR THE FUTURE

With more than 15 years of experience in smart drug delivery solutions, Aptar Pharma recently launched its two new electronic drug delivery e-Device platforms: e-Dose Counter and e-Lockout.

“Smart devices will have an important role to play in integrated healthcare provider systems as these start to be deployed in the mid- to long-term future,” said Joachim Koerner, Vice-President e-Device platform R&D, Aptar Pharma Prescription Division. “With all these innovative developments, Aptar Pharma is able to offer robust and cost-effective solutions for enhancing patient compliance.”

E-DOSE COUNTER

e-Dose Counter (see Figure 1) is a cost-effective solution which meets EU and US regulatory recommendations for nasal and sub-lingual spray delivery of controlled substances. The use of electronics allows the counting display to be large and highly visible making it suitable for patients of all ages and with different conditions and disabilities. Electronics can also provide patient comfort features such as acoustic feedback and flashing displays to inform and warn.

The lightweight, robust device promises cost savings through improving compliance. It is IP protected yet customisable, thus representing an ideal means for achieving product differentiation and effective lifecycle management.

E-LOCKOUT

In addition to counting and displaying the number of actuations, e-Lockout (shown in Figure 2) also prevents the device from being



Figure 1: e-Dose Counter incorporates the benefits of a dose counter with the advantages that an electronic device has over a purely mechanical system.

“USER STUDIES CONFIRM THAT ELECTRONIC DRUG DELIVERY DEVICES ARE NOW AS WELL ACCEPTED BY THE MAJORITY OF CONSUMERS AS SMART PORTABLE DEVICES SUCH AS PHONES, GAMES, AND PADS”

used for a specific period after a predefined number of actuations. Its purpose is to promote compliance and specifically also to prevent overdosing, and it can meet regulatory requirements for controlled substances.

Its locking system, which warns of overdosing, is recommended by regulators for nasal and sub-lingual spray delivery of controlled

substances used in breakthrough pain management. In addition to counting and displaying the number of actuations and locking, some of the key features which can also be incorporated into e-Lockout include patient aids and feedback as well as data transmission.

These two novel e-Device platforms are aimed at improving patient compliance.



Figure 2: e-Lockout promotes compliance and prevents overdose of controlled substances.

MULTILINGUAL VERSIONS OF THE APTAR PHARMA WEBSITE NOW LIVE!

When Aptar realigned its activities in 2010, including placing all of its pharmaceutical activities under the brand Aptar Pharma, the company launched a new web page. Since that time, web traffic has doubled and continues to grow, driven in part by strong demand from around the world including the emerging markets.

In response, Aptar developed and has now launched versions of its originally English webpage in four additional languages: Chinese, French, German and Spanish. Access in more languages, including Portuguese, is planned for 2014.

A GLOBAL LEADER

Aptar Pharma was one of the pioneers in the local manufacturing of drug delivery systems.

Its production facility in Argentina, which was opened in 1981, serves the pharmaceutical markets of Central and Latin America. The company started its manufacturing operation in Suzhou, China in 1996 to serve both

China and other Asian countries, and was the first company licensed to manufacture spray and aerosol drug delivery devices in China. In early 2012, a new manufacturing site was opened in Mumbai, building on 22 years of presence in India.

In Latin America and Asia, Aptar Pharma has been market leader for several years now, and will continue to expand its business in these local markets, which require adapted communication tools and materials.

Visitors to the new web pages now have easy access in their own languages to comprehensive information about Aptar Pharma. These information resources include a company snapshot with Aptar's identity and strategy as well as key facts and figures; detailed information about our products and services and their therapeutic areas of application; scientific materials for academics and researchers; and media resources for the press.

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COMPANY PROFILE PHILLIPS-MEDISIZE



Partnerships Built on Innovation

Phillips-Medisize is a leading global outsource provider of design and manufacturing services to the medical device and diagnostics, drug delivery and commercial markets, and has a history of manufacturing complex drug delivery devices such as inhalers, injection pens and safety syringes. The company has produced dry-powder inhalers (DPIs) since 1985, and has been involved in the development of about ten different inhaler programmes. Phillips-Medisize was the development partner for the first DPI, but since then our speed of turning a new inhaler platform design into clinical trials has increased significantly.

Large pharmaceutical companies require functioning inhalers before they make decisions concerning new inhaler platforms. Good ideas and drawings are not enough.

The company's strategy has been to develop its services continuously in order to keep up with these challenges. To deliver speed in all the development phases, it has invested in the very fast manufacturing of both one and multicavity tools.

As this service is combined with the best metrology service available on the market, the customer gets components and devices in record time. Having all the critical services in-house – such as design and development, tool manufacturing, metrology and injection moulding – alongside a long experience of assembly automa-

tion, has been a resoundingly successful strategy.

Customers are satisfied with seeing their new devices turn into full production in a continuously shorter time period.

Thanks to Phillips-Medisize's successful implementation of the strategy of delivering fast development programmes, customers have awarded it with new business. This is why the company added a 6,000m² expansion to its facility in Kontiolahti, Finland, in February 2013. This state-of-the-art facility focuses on the production of complex drug-delivery devices such as inhalers, injection pens and safety syringes, manufacturing various products from multicomponent drug delivery devices in prototype form to finished drug-delivery devices in a high-speed automated production environment.

The expansion was driven by new opportunities that Phillips-Medisize has been presented with over the past 12 months, as well as, to support increased global demand for devices with precise dosage drug-delivery requirements.

Phillips-Medisize has annual sales of more than \$500 million (£325 million), with 75% of the total revenue coming from drug delivery, medical device and diagnostic products such as disposable insulin pens, glucose meters, speciality inhalation drug-delivery devices, single-use surgical devices and consumable diagnostic components.

COLLABORATION

When product launch success depends upon speed to market, drug and device companies benefit by joining forces. Such partnerships can free pharmaceutical and biotech companies to focus on their core competencies, while leveraging

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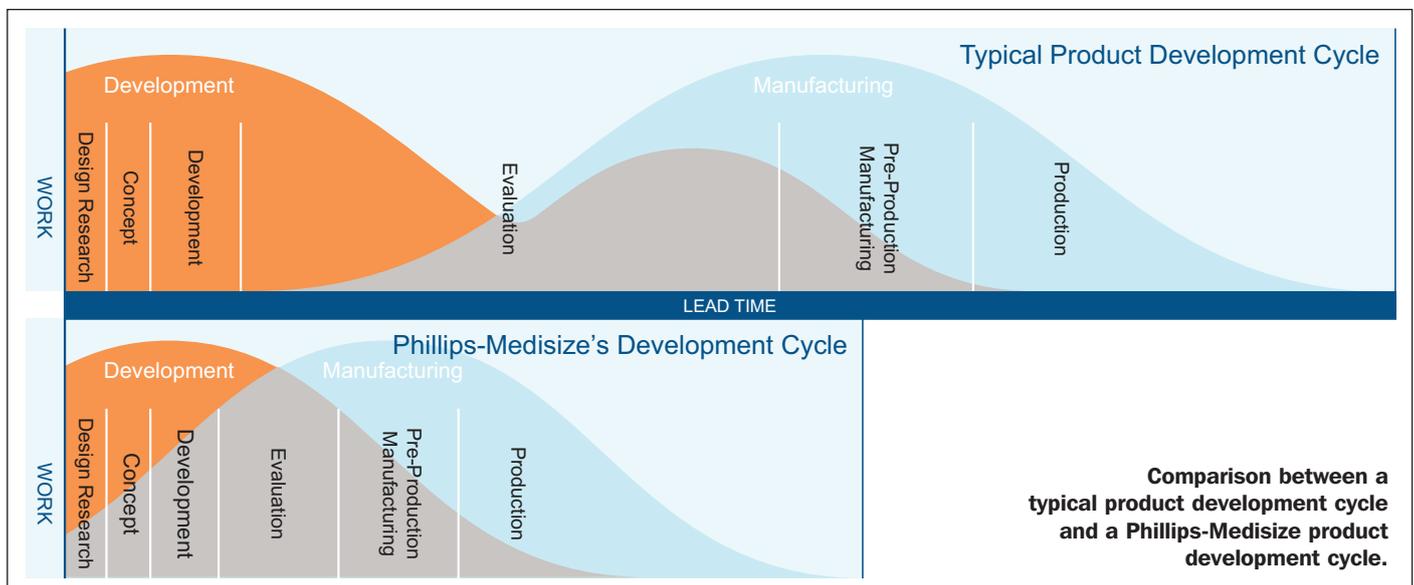
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their suppliers' existing, proven, regulatory compliant manufacturing processes and infrastructure. Early collaboration, from initial design concept phase, allows the device company partner to help anticipate potentially problematic areas that can occur during pilot production, clinical trials and eventual high-volume manufacturing.

Project success, and the ability to control the many variables in product development, depends upon the ability of drug companies to select the right device manufacturing partner, with the right mix of development support and commercial manufacturing service offerings, to help guide the project. This target is best met by working with a single supplier able to handle and package drugs, demonstrate complete knowledge of the complexities of medical product development, and offer a full range of engineering and product development services.

By applying adequate due diligence in choosing their partner, pharmaceutical and biotechnology companies can improve the odds of launching a successful new drug product into the marketplace – on time and on budget.



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INTEGRATED PACKAGING & FILLING SOLUTIONS FROM COSTER

With Coster celebrating its 50th anniversary this year, Bianca Cavalli, Sales & Marketing Manager of Coster's Pharma Division, gives a brief history of the company's origins leading to its position today as a major multinational manufacturer of dispensing systems and filling machines, in particular for inhalers and nasal pumps.

The year 2013 represents a milestone for Coster: the 50th anniversary of the Group, founded in 1963. In the course of half a Century the company has become an international firm positioned at the cutting edge in the development and production of dispensing systems including pumps, aerosol valves, BOVs (Bag-On-Valves) and MDI valves & inhalers (Figure 1). These products are suitable for nasal, oral, topical and pulmonary applications. In addition to primary and secondary packaging, Coster produces fill-

present itself as the only company able provide an integrated solution to its customers, who can enjoy the benefit of dealing with a single partner offering a 360° solution.

BRIEF OVERVIEW: A SNAPSHOT OF COSTER'S 50 YEARS SINCE ITS FOUNDING

After 50 successful years full of achievements, Coster finds itself in good shape.

Founded as a small, local company, it started producing only filling machines. The dispensing systems came at a later stage. In the course of these five decades, Coster has undergone a series of significant changes that have seen it develop into a multinational with 900 employees around the world and a global turnover in 2012 of €178 million (£149 million). In 2006 its involvement in pharmaceuticals became more structured and proactive when the firm decided to devote specialised resources and significant investments to this

“SIGNIFICANT AND SUSTAINED INVESTMENT IN INNOVATION, TO WHICH APPROXIMATELY 9% OF TURNOVER IS DEDICATED, HAVE ALLOWED COSTER TO EQUIP ITS PRODUCTION SITES WITH THE MOST ADVANCED TECHNOLOGIES, INCLUDING WAREHOUSES WITH VERTICAL ROBOTICS AND LASER-GUIDED VEHICLES”

ing machines for pharmaceutical aerosols and liquids, which are fit for R&D purposes and/or large production runs. This allows Coster to

sector. Currently, turnover from the Pharma Division represents just under 10% of the Coster Group total. The last five years, how-

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Figure 1: Coster is at the cutting edge in the development & production of dispensing systems including nasal pumps & inhalers.

ever, have seen double-digit growth. Coster remains a highly diversified global group in terms of its products and its geographical reach, which assure it considerable stability while enabling continued growth, even under current economic conditions.

MANUFACTURING STRENGTH

In order to meet the needs of its customers, who operate in diverse and fairly competitive markets, Coster has developed a vast and efficient manufacturing organisation that is well structured and diversified, with fifteen production facilities distributed across four continents: eight in Italy, of which seven are located in the Trento area – where the firm was founded – and one in Lombardy; three in Europe (Holland, Spain and the United Kingdom); two in Asia (India and Malaysia); one in the US; and one in Argentina. In addition there are two sales centres, in France and Germany, and dedicated pharmaceutical representatives wherever Coster is not present with its own production site. The facilities, which are automated and “intelligent”, are characterised by a vertical organisation governing the entire production cycle and dedicated – with an eye to optimal focus – to a specific type or family of products. Significant and sustained investment in innovation, to which approximately 9% of turnover is dedicated, have allowed Coster to equip its production sites with the most advanced technologies, both in terms of moulding and assembly as well as inventory and internal logistics, including warehouses with vertical robotics and laser-guided vehicles.

In a number of facilities the company applies the logic of lean manufacturing (“Kanban”, for

“WE HAVE SEEN FURTHER DEVELOPMENT OF EMERGING MARKETS, WHERE A TRANSITION IS UNDERWAY FROM THE BRIC COUNTRIES (BRAZIL, RUSSIA, INDIA, CHINA) TO THE TREC COUNTRIES (TURKEY, RUSSIA, UNITED ARAB EMIRATES, CHINA)”

re-integration of raw materials) and pays strict attention to matters related to sustainability and the environment, enforcing a rigorous policy of corporate responsibility. Among the resources dedicated to pharmaceuticals it is important to point out the cleanroom for MDI valves and nasal saline actuators (see Figure 2), classified ISO 7 ‘at rest’, according to ISO 15378:2011, which refers specifically to GMPs applied to

primary packaging components used for medicinal products. It is worthwhile to note that Coster has recently been awarded a Type III Drug Master File (DMF) for MDI valves (Figure 3).

Investments continue and the end of 2013 will see the addition of a second cleanroom, dedicated specifically to pharmaceutical pumps. This second room is also classified ISO 7 ‘at rest’ and is currently nearing completion.



Figure 2: The cleanroom for MDI valves and nasal saline actuators is classified as ISO 7 ‘at rest’.



Figure 3: Coster has recently been awarded a Type III Drug Master File (DMF) for MDI valves.

PRIMARY MARKET, WITH REGARD TO PHARMA PRODUCTS

Coster Pharma's customer portfolio is broad, diversified and continues to develop, comprising organisations of all types and dimensions (from pharmaceutical and parapharmaceutical companies, generics companies, R&D firms, CMOs, etc). As noted earlier, but worth emphasising, Coster has seen a significant growth for pharma products in recent years. Distribution is currently split between Europe at 60% and the rest of the world at 40%. Of the latter, just under 35% is in the Americas, and marketing strategy focuses on two clearly defined directions. On the one hand we have seen further development of emerging markets, where a transition is underway from the BRIC countries (Brazil, Russia, India, China) to the TREC countries (Turkey, Russia, United Arab Emirates, China), with considerable attention being paid to the so-called "Future 22", countries with a particularly high growth rate and of interest as export target markets. On the other hand there is penetration into highly regulated markets. In its proactive search for new customers and new markets, Coster is also present every year at the most important international trade exhibitions.

STRATEGIC & OPERATIONAL APPROACH

Customer satisfaction is an absolute priority for the firm: all customers are of equal importance and subject to the same sort of attentive handling, regardless of their size. With numerous offices around the world, Coster is

able to guarantee efficient and effective service in responding quickly and specifically to the different requirements of diverse markets and customers. This is not just a matter of geographic proximity but refers as well to a flexible approach that does not seek to "impose" a product but attempts rather to understand the specificity of local conditions and the real needs of the customer in order to put together the most suitable solution. The same goes for post-sales service (installation, start-up, validation, maintenance), which in some countries and for some products (such as filling machines) become as important as – or even more important than – the product itself. Another important advantage, much appreciated, is the availability of two labs, which allows Coster to offer additional services to its clientele.

LOCATION & OPERATION OF COSTER LABS

One Lab is located in Pero, on the outskirts of Milan, Italy, and the other is in Calceranica al Lago, in the area around Trento (Figure 4). Their purpose and principal activities consist in carrying out tests for compatibility between formulations and valves and pumps; in helping customers choose the most appropriate products to meet their needs; in supporting the "transformation" of a semi-solid or liquid formulation into an aerosol format, which requires specialist know-how not available to all customers and for which Coster is a recognised authority. In conclusion, Coster presents itself and is recognised in the global pharmaceutical market as a company able to offer high-quality products and services as an integrated solution, specific and custom-designed, which includes primary and secondary packaging components, filling machines and formulation/reformulation services.

SCIENTIFIC COLLABORATION

Coster's strong orientation toward customer service and innovation finds concrete expression in significant collaborative projects with pharmaceutical companies and prestigious scientific institutes and universities. One example is the Pharmaceutical Faculty of the University of Parma, where Coster has installed semi-automatic filling machines for MDIs, which make it possible to perform analyses with APIs, analytic tests and stability studies.



Figure 4: Coster's R&D facility and technical headquarters at Calceranica al Lago, Italy.



PRESSPART

MODIFYING MDI CANISTER SURFACES TO IMPROVE DRUG STABILITY & DRUG DELIVERY

Hydrofluoroalkane (HFA)-based propellants are widely used in modern metered-dose inhalers (MDIs), due to their lack of hazardous and environmentally-damaging effects. However, an HFA's active pharmaceutical ingredient can interact with the canister substrate, causing deposition of the drug to the canister walls, or interact with the solution, causing degradation and resulting in increased impurity levels. Over the past few years, a number of surface coatings have been developed that can be applied to MDI canisters and valve components, to protect the contents from deposition and degradation. More recently, plasma processes have been developed to modify and improve the surface energy performance of a MDI canister. This approach has a number of advantages to alternative coatings but requires careful optimisation to ensure the highest quality finish and MDI performance. Richard Turner, Business Development Director, Presspart Manufacturing Ltd, explains.

MDIs are commonly used to deliver drugs for treating respiratory and nasal disorders. The drugs are administered by aerosol, in suspension or solution, with a liquefied gas propellant. For over 50 years, chlorofluorocarbons (CFCs) were the pro-

specifically HFA 227 and HFA 134a. These substances are not ozone-depleting, they are also non-flammable and chemically inert, making them ideal candidates for use in medical products. However, some properties of these compounds are substantially different from those of the CFCs traditionally used in MDIs.

The surface properties of a device can have an important effect on the device's interactions with its most immediate environment and substances with which it comes into contact. As a result, the device's surface chemistry has a vital role on the surface functionality and, therefore, overall performance of the device and drug.

When HFA-MDI drug formulations are in suspension, interactions with the canister substrate can cause deposition of the drug on the canister walls or on exposed surfaces of the valve components. Interactions with solutions more commonly cause degradation, resulting in increased impurity levels. In both

“A VARIETY OF PLASMA TREATMENTS HAVE BEEN TRIED IN THE PAST BUT THESE HAVE FAILED TO PENETRATE THE MARKET DUE TO POOR SCALABILITY AND COST VIABILITY. HOWEVER, ALTERNATIVE DEVELOPMENTS HAVE BECOME AVAILABLE THAT MAKE PLASMA A REAL CHOICE FOR MDI CANS”

pellants of choice, but these have now largely been phased out, in line with the Montreal Protocol.¹

Replacement propellants have been developed over the past two decades based on HFAs,



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cases the interaction leads to a reduction in the drug content in the formulation, resulting in the patient receiving less than the prescribed dose.

RANGE OF COATINGS

Applying a suitable surface coating to the MDI components improves the stability of the formulation as well as the product performance, and helps to extend the product's shelf-life. A range of coatings have been developed that can be applied to both the canister and valve components to protect the contents from deposition and degradation.

Commonly used coatings include barrier coatings, such as anodisation of the canister, to change the surface characteristics and ultimately act as a protective barrier for sensitive formulations. Various low-surface-energy coatings are available for suspension formulations. For example, a surface treatment has been specially developed for deep-drawn 5052 aluminium canisters (Figure 1) and is suitable for budesonide HFA; and new coating compounds have been developed that prevent certain HFA-containing drug formulations (for example, salbutamol) from interacting with the MDI and adhering to canister walls.

Fluorocarbon polymers are commonly used to coat the interior canister surfaces to eliminate adhesion or deposition of salbutamol (albuterol) on canister walls. Salbutamol is widely used with other MDI drugs, particularly beclomethasone dipropionate. Fluorocarbon polymers used in coatings are commonly made from multiples of one or more of a variety of monomers; particularly preferred coatings tend to be pure perfluoroalkoxyalkylene (PFA), and blends of polytetrafluoroethylene (PTFE) and polyethersulphone (PES), due to their relatively high ratios of fluorine to carbon. In addition, coatings that combine fluorocarbon polymers with non-fluorocarbon polymers (such as polyamides) are used for certain formulations to improve adhesion of the coating to the canister walls; other coating types include epoxy-phenol resins.

COATING TECHNIQUES

Standard metal coating techniques can be used to pre-coat the metal substrate and cure it, prior to shaping the metal into the components (for example, through deep-drawing or extrusion). This pre-coating method has the advantage of being well suited to high-volume production.

Other coating techniques include: spraying the insides of preformed cans; dipping; or electrostatic dry-powder coating, followed by curing. Many of these processes require high temperatures



Figure 1: Aluminium MDI canisters.

(up to 400°C when curing), which can create additional costs and complications. Furthermore, only the most robust canisters (that is, those produced through deep-drawing) should be subjected to such high temperatures, as less robust canisters can become unrolled or suffer other morphological changes under these conditions.

PLASMA PROCESSING TECHNOLOGIES

More recently, gas plasma-based processes have been developed to modify and improve the surface energy performance of an MDI canister. Gas plasma processing is an industrial technique that is carried out in a vacuum to coat a wide range of substrate materials. The process involves constant or pulsed excitation of gas by either radio frequency (RF) or microwave field to produce an energetic plasma.

The process creates an ultra-thin layer that protects against degradation, deposition and corrosion. It is a low-temperature process (<75°C for metallic substrates and <45°C for polymeric substrates), and is ideal for uniform treatments of components with complex shapes,

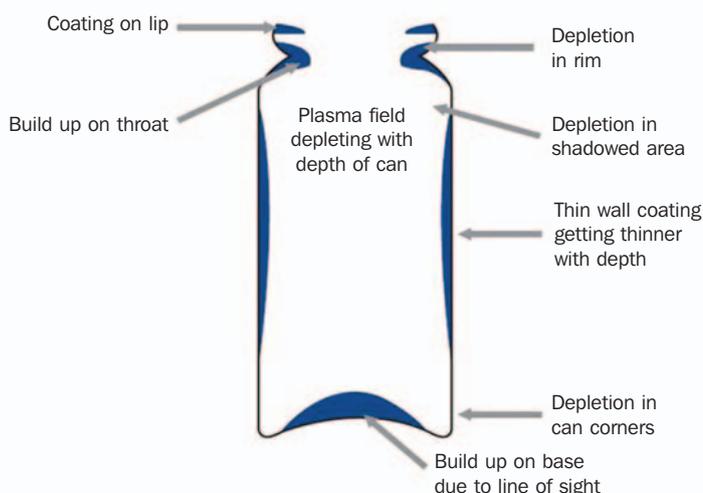
including small components in large volumes. The coating adheres well to the component substrate because the plasma process cleans the component surface while in the vacuum, resulting in an ultra-clean substrate-coating interface.

Using gas plasma to tailor the surface chemistry has the advantage of providing uniform surface treatment without changing the properties of the bulk material. The process can be used to change the outermost layers of the material only, without polymerising a coating, resulting in modifications to the functional chemistry. These modifications can be used “stand-alone” or with the addition of a subsequent surface coating through a single process cycle, depending on the application and desired properties.

OPTIMISING THE PLASMA PROCESS

Plasma processing of MDI canisters can bring multiple benefits to the MDI performance, helping to reduce drug deposition and also to improve the stability of formulations where interactions with the aluminium substrate would lead to product degradation and reduced shelf

a) CAN COATED BY TRADITIONAL PLASMA PROCESS



b) CAN COATED BY NEW PLASMA PROCESS

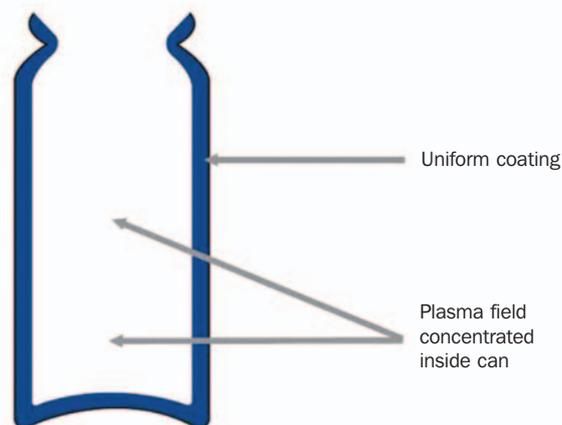


Figure 2: a) Traditional plasma processing does not ensure a uniform coating to internal wall of the canister. b) The new plasma process gives a uniform coating to canisters.

life. However, plasma processing for MDI canisters needs to be highly controlled to ensure complete consistency of treatment and uniformity of coating to the internal walls of the canisters.

Plasma chemistry is critical to the performance of the coated canisters – the right choice of precursor chemistry enables a robust process with excellent performance. A variety of plasma treatments have been tried in the past, including single- and dual-layer technologies with a range of monomers, but these have failed to penetrate the market due to poor scalability and cost viability. However, alternative developments have become available that make plasma a real choice for MDI cans.

A cost-effective process has been established using an optimised plasma chemistry consisting of an intrinsically robust monomer, highly ionised to form a high crosslink density. The ultra-pure gases and monomers do not contain any solvents, so do not produce any waste by-products. The result is a coating technology without the extractable issues potentially encountered with some polymer systems.

It is critical that plasma processing achieves complete and consistent coating across the entire surface of the inside of the canister.

Traditional plasma processes, RF or microwave, are particularly difficult to control when internal surfaces are to be treated. Poor penetration of plasma ions with low energy results in non-uniform, thin or porous coatings with poor performance. Increased ion energy to aid depth of can penetration gives rise to ion etching at the can neck and a more “line-of-sight” process.

This partial “line-of-sight” process leads to non-uniformity/thickness variation in such geometries (see Figure 2a). For thin nanometre coatings on MDI cans this is observed as striations in colour or colour bands down the can. With the best compromise the coating builds up around the canister lip, throat and base, with depletion at the rim, shoulders and can corners.

More recently, an improved process has been developed that eliminates the issues associated with typical plasma system designs. Using proprietary gas/monomer delivery configurations and electric field control (designed specifically for can coating geometry), uniform coatings can be deposited (Figure 2b).

Dedicated system design configurations mean constant, high deposition rates with extreme reproducibility in terms of coverage, chemical speciation and product performance. The unique

combination of process equipment design and precursor monomer means the technology is now scalable to handle the throughput and commercial demands of the MDI world market.

This process has been used to develop several different plasma coating options that successfully prevent drug deposition on the can walls, and prevent drug degradation in solution or suspension. Examples include surface treatments for budesonide, formeterol, fluticasone propionate and beclomethane dipropionate, amongst others.

CONCLUSIONS

Gas plasma processing offers considerable advantages in the coating and treating of MDI canisters for improving the stability of the formulation and extending product shelf-life. In addition, the ability to plasma process high volumes of the canisters fulfils the high volume demand from the MDI market.

REFERENCE

1. *Montreal Protocol on Substances that Deplete the Ozone Layer* (<http://ozone.unep.org>).



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