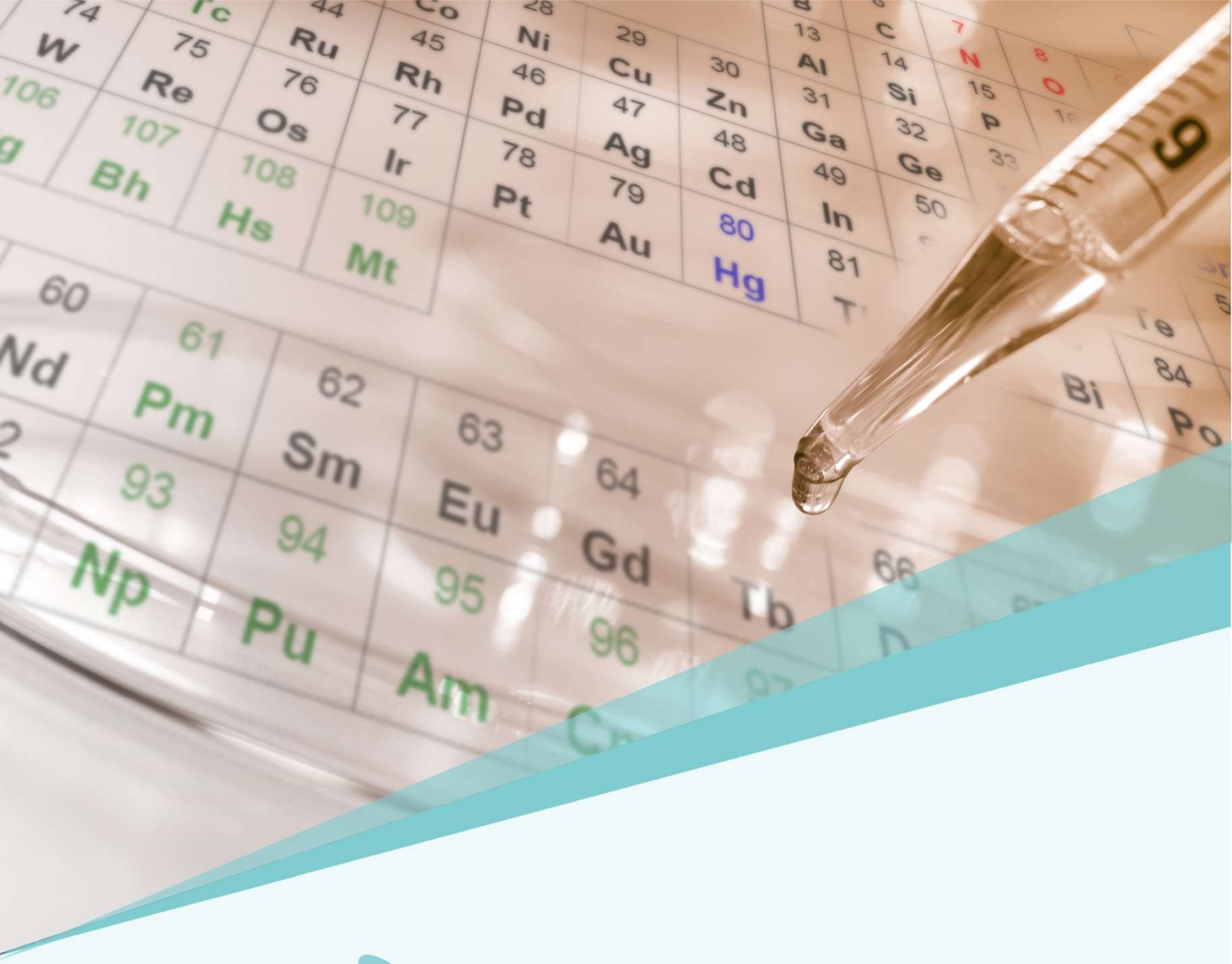

eu.reca

European Respiratory Cluster Antwerp

Innovative Formulation for Inhaled Drugs

DFE pharma

KERRY
Leading to Better

ORIENTO

ULB

INTRODUCTION

The organization of this workshop, on behalf of eu.reca vzw, was initiated by Stefano Console, who is the ambassador for the formulation field within eu.reca. This workshop was co-organized with Prof. Karim Amighi, director of the Department of Pharmaceutics and Biopharmaceutics at the Université Libre de Bruxelles (ULB).

The European Respiratory Cluster Antwerp is a knowledge platform focusing on the lungs. Progress can be made through open debates amongst experts, sharing their knowledge in modern technology, unmet medical needs and industrial capabilities. This cluster is related to prevalence of disease, progress in inhaled medication, accuracy of drug deposition, outcomes of treatment and environmental impact on lung health. Eu.reca holds open discussion forums about any topic in the respiratory field where there is potential for improvement.
The main power of eu.reca is to bring access to modern technology and share knowledge for all its members and give them appropriate support in developing their projects, ideas and concepts. With a focus on lungs, eu.reca installed a hub that can help companies in creating new treatment opportunities for lung diseases from the concept idea all the way to the commercialisation.

The main value of eu.reca remains its members. It brings together experts in inhalation from academic institutes, technology organisations and industry. In addition to this, eu.reca also offers academic, logistical, management, financial and technological support to its members.

The innovative formulation for inhaled drugs workshop was divided into two main parts:

- Dry Powder Inhalers and carriers
- Manufacturing processes of Dry Powders

DRY POWDER INHALERS AND CARRIERS

Each session started with three expert presentations and was followed by an interactive thematic round table conference in which all stakeholders took part.

There are two main kinds of formulation for dry powder inhalers (DPI): the carrier-free and the carrier-based formulations.

CARRIER-BASED FORMULATIONS

Carrier-free or carrier-based formulations?

These are interactive blends in which the carrier helps to improve the handling, dispersing and metering of the drug. The carrier generally consists in coarse particles (50-250 μm), but fine particles or even ultrafine particles can be used as an adjuvant in association with the carrier.

For example, carriers such as lactose (coarse, fine), other sugars (mannitol, glucose, trehalose), amino acids (leucine) or even lipids (Solid Lipid Microparticles) can be used.

The process development is complex but well-known and the formulations are generally simple and well tolerated. Nevertheless, some limitations still remain in terms of the control of the release of the API and its deposition and retention in the lungs. Also, some irritation can occur subsequent to the delivery of carrier-based DPI's to the lungs.

CARRIER-FREE FORMULATIONS

These formulations are based on the use of micron-sized particles containing the API alone, the API particles associated with excipient(s) and composite API-excipient particles. They are obtained by particle engineering using different production technologies such as (jet) milling, homogenization, spray (freeze) drying and supercritical fluid techniques.

Excipients proposed in the literature include sugar, amino-acids, surfactants, lipids, magnesium stearate, polymers and cyclodextrins. There are a limited number of excipients that are accepted for inhalation but many of them can be considered as acceptable excipients for inhalation as they are already used for other routes of administration. The use of excipients that are not already accepted for inhalation requires the organization of long and costly toxicological studies.

There is no general and universal answer to the question of whether to use either a carrier-based or carrier-free DPI. The goal is to obtain an optimized deposition with an optimized formulation that is adapted to its device.

A way to answer this question is to keep in mind that for asthma and COPD, the active pharmaceutical ingredient (API) is used in a lower concentration than for other drugs. This means that the API needs to be diluted, and therefore the use of a carrier-based DPI is still the preferred solution. But for other diseases, when the API concentration is higher, or a better control of particle deposition or release in the lungs is required, it is important to take other parameters than the dilution and the processability of the DPI product into account to answer to this question and determine the appropriate formulation strategy.

What are the parameters that influence the DPI performance?

PARAMETERS INFLUENCING THE AERODYNAMIC PERFORMANCE

The aerodynamic performance of DPI formulations can be evaluated using impactors described in pharmacopoeia (e.g. NGI, ACI), by determining the *in vitro* particle deposition and the Fine Particle Fraction (FPF, particles below 5 µm). This performance is influenced by different factors such as the carrier material, its particle size distribution, roughness and its morphology. The size and the morphology of the API as well as the addition of fines, the preparation of blends (process, order of addition of ingredients, properties), the storage conditions (temperature, humidity) and the type of device used can also critically influence the performance of these blends by modifying the FPF.

The fact that these parameters influence the properties of DPI formulations also means that these parameters can be used to optimize and improve their aerodynamic performance. The most important criteria is to find the best balance between adhesion and dispersion forces present in the drug-carrier interactive blends.

The development of DPI's requires consideration of three major components: the formulation, the patient and the device. Each DPI needs to be formulated in the best way to adapt to the patient's inspiratory force. Also, an appropriate use of the device by the patient (i.e. by appropriate training) is important to improve lung deposition. Last but not least, the performance of the device needs to be as independent as possible from the patient's inspiratory force. It must be chosen depending on the population type (e.g. children and elderly people) and the respiratory capacity of the patient.

EXAMPLE OF INNOVATIVE DPI DEVELOPMENT

Different innovative DPI formulations (carrier-free and carrier-based) were recently developed by the ULB and required optimization such as:

What can we do today in terms of innovative DPI powders

- The stabilization of tiotropium in an amorphous state (Braltus®) using an interactive blend with lactose, resulting in the reduction of the drug content for the same efficiency.
- The association of two drugs in the same particle in a stabilized amorphous form and presenting a co-deposition and co-dissolution (tiotropium and indacaterol).
- The optimization of the in vitro and the in vivo deposition profiles of tobramycin by developing a new lipid carrier.
- The increase of itraconazole solubility, lung pharmacokinetic profiles and prophylactic efficacy in a murine model of lung aspergillosis by using a solid dispersion-based DPI.
- The development of PEGylated solid lipid microparticles with prolonged release and lung retention for the local delivery of cisplatin as an anticancer drug to treat lung cancer.
- The DPI based on paclitaxel containing nanoparticles targeting lung cancer cells using a folate grafted excipient.
- The development of large porous particles characterized by a large geometric diameter and a low density. These two characteristics combined together ensure a good lung deposition while escaping alveolar macrophages:
    - Torus Particles
    - Trojan Particles: Nanoparticle-based Microparticles

What about the Trojan particles?

- The administration of Pyrazinamide-based Trojan particles to mice showed that there is no difference between the use of the pulmonary or intravenous route. This is due to the high hydrophilicity of the drug.

- The administration to mice of a lipophilic drug particles showed that the passage into the bloodstream is low and that the lung retention was high as well as the alveolar content.

The development of innovative DPI's seems to be achieved: targeting specific regions in the lung, adapting the formulation to the disease need, optimization of the formulation characteristics to obtain selected in vitro and in vivo profiles.

Therefore, several ideas surfaced. Have we really reached the maximum in terms of optimization? Are the animal models representative enough of the human diseases? Don't we need to see the development from another point of view and therefore adapt the DPI formulations? Are we far enough in terms of personalized medicine? Can we imagine having the devices on the one hand and the formulation on the other and then combining them depending on the patient's need? How can the regulatory pathways adapt to this innovation? What about precision medicine?

DRY POWDERS MANUFACTURING

MICRONIZATION BY SPIRAL JET MILLING

Micronization can be performed using a fluid energy mill based on the acceleration of the particles using compressed nitrogen or air. Size reduction is achieved mainly by particle-particle collision.

As the size of the particles is reduced, other particles properties such as amorphous content and surface morphology also change during the milling process. In order to control them, the feed rate and the grinding pressure should be monitored.

Micronization by jet milling or spray-drying?

SPRAY-DRYING

The spray drying is a technique used for particle engineering. It is an instantaneous and continuous solvent evaporation process involving a liquid feed (solution or suspension) atomised as small droplets in a heated gas generating dry particles which are mostly amorphous.

The measured parameters are the gas flow, the inlet and the outlet temperature and the pressure drop.

Moreover, this technique is appropriate for the large-scale development of DPI's. In that context, a recent concept has been developed involving a parallel set-up with three units that are able to work independently.

Micronization is widely considered as a step towards the perfect formulation in terms of particle engineering. It is a technology mostly employed for carrier-based DPI's and thus an additional step after micronization is required: blending. Blending is a crucial step where particles with very different characteristics (micronized API being very fine, carrier(s) being coarser) and different amounts must be perfectly blended to guarantee the therapeutic single dose for the patient.

The manufacturing process includes many aspects: equipment design, technology upgrade, particle size distribution and morphology modelling, physical attributes targeting, design of experiments and scale up studies, but also industrialization. Yet, there are a lot of possibilities for the development of innovative DPI's using spray-drying, mainly regarding carrier-free formulations.

The major strengths of spray-drying are related to the fact that it can produce dry and homogeneous particles with a defined size distribution and shape and can allow them to target specific pulmonary sites. No blending is needed if the carrier-free DPI formulation is well developed. Plus, this process can easily be scaled-up.

In order to visualize particle formation from droplets while they dry during the spray-drying process, different models can be used. As an interesting example, Leidenfrost droplets were deposited on a heated plate and visualized using a fast camera and an optical device.

How do porous particles dry during spray drying?

To understand the particle formation mechanism, it is important to focus on the Peclet number (P_e) of the drying system. When the P_e is smaller than 1, the evaporation rate of the solvent is slow compared to the diffusion rate of the solute. This allows the solute to diffuse toward the center of the droplet to form small non-porous particles (e.g. lactose spray-dried from a water-ethanol 70:30 v/v mixture). Whereas, when the P_e is higher than 1, the drying of the droplet is fast and a shell is therefore formed on the surface of the droplet, leading to porous particles. In these conditions, for high P_e values, larger particles with low density can be obtained which can be wrinkled or hollow (e.g. nanoparticles of polystyrene latex with a P_e number 200-fold higher than lactose).

The composition of the solvent and more particularly its volatility influences the particle shape. When polystyrene nanoparticles are spray-dried in water, doughnut shaped particles which are characteristic of buckled shells, are obtained. Whereas, the spray-drying of the same particles in ethanol-water mixtures leads to the co-existence of buckled shells and hollow particles. The buckling of elastic shells occurs when the pressure across the shell exceeds a threshold. In fact, in the beginning of the drying, the shell is viscous and not elastic as there is an evaporation of the solvent. During the drying, the capillary forces try to put the particles together, but the electrostatic repulsion forces try to separate them. When the capillary forces overcome this repulsion, the shell becomes elastic, and therefore a shrinkage is observed resulting on a decrease of viscosity.

Therefore, by changing the solvent composition, the morphology of the particles is changed, which influences their delivery to the lung and drug release.

RESPIRATORY POWDER FILLING

While the filling processes for pressurized metered-dose inhalers (pMDIs) are quite well standardized, this is not the case for DPI's. The DPI filling always relies on a volumetric dosing system. The aim is to obtain a mass accuracy as recommended by pharmacopeia, which still remains difficult to achieve because:

What makes powder filling a critical method for DPI formulation development?

- The flowing of DPI's is poor, meaning that they tend to form agglomerates during agitation.
- The gravitational forces are not enough to achieve uniform filling of dosing chambers.
- The volumetric techniques add forces during the dosing step: mechanical deformation/compaction, vacuum or pressure drop and energy.
- The DPI's are all different: Carrier-based DPI's with lactose monohydrate, hollow microspheres, etc.

The filling can be performed using a dosator, a vacuum drum, a membrane, a screw auger or a disc filler.

Which technique is to be preferred over another depends on the device (i.e. capsule, blister or reservoir based DPI's) and on the DPI properties. Therefore, powder filling must approach powders as diverse and multi-particulate systems.

The interactions between the filling system and powder have to be understood as well as the influence of the "dosing force" on the final drug product performance.

The powder filling needs to be considered during the DPI development. The more open the dialogue between the stakeholders can be early on, the greater the chances of success.

The key to success is to cooperate from the start and share the know-how. One solution would be the involvement of experts in the early phase of development. "What should be considered before the next step?". The idea is to highlight things we need to focus on and consider all the DPI critical points during development. This should be a multidisciplinary approach that takes into account the complexity of the product and the interaction between the patient, the device and the formulation.

Many factors need to be checked: pharmaceutical ingredients and DPI characteristics, toxicity on tissue, local versus systemic delivery, innovation of the formulation, variability of the delivered dose, acceptance by the patient, and so on.

CONCLUSION

During this workshop, the topics covered focused on the viability of DPI's, the formulation approaches, and the technologies required to manufacture them. DPI's are one of the first choices for many reasons (e.g. easy to use and carry, large dose delivered, long-term stability).

The fundamental aim is to cure lung pathologies, but the lung is a sensitive tissue. There is a balance between efficacy and side effects to consider for each case. Therefore, it is necessary to understand what is actually occurring in the lungs and to adapt DPI's to the patient's needs.

Many ideas emerged from the discussion. Several aspects have to be considered in developing the appropriate formulation strategy. Indeed, the formulation of dry powders is not the only key factor for producing the optimal product. The link between the formulation, the device and the patient has to be considered because one does not go without the other two. Moreover, there is a lot of knowledge about each part, but this knowledge is not shared enough between the stakeholders.

Other critical aspects were also highlighted. These included the large numbers of available devices that require the patient's adaptation and education, the necessity to be sure that industries and regulations understand and adapt to innovation, or the lack of interconnection between the stakeholders. A solution would be the creation of a process window where the formulation is critically reviewed to ensure that it is appropriate for the next steps along with working with a team with knowledge of the technology. Knowledge of the different development steps is crucial to qualify and monitor every parameter because it has an influence on the product obtained at the end of the process. Moreover, it is important to find the reference points to be sure that is possible to scale-up or transfer to an automatic line. Another point concerns the creation of a dry powder database which could be time saving, but also the use of techniques to help with formulation such as mathematical tools, medical tools or 3D models.

Sciences are evolving and discussions are helpful. The members of this Eu.reca session mentioned other experts who could be welcomed to further explore topics such as generic formulators, members of device companies or patients who could help to better identify issues linked to the use of inhalation products. Although innovative DPI's may seem to be well-developed products, there is still a lot of work to be done in optimizing formulations for inhalation due to their high complexity. Further challenges could be the creation of personalized DPI's or practising precision medicine in the inhalation field. This can be made possible as long as the stakeholders share their knowledge.

Science are evolving - Interdisciplinary discussions are needed.

EXPERT OPINION:

PAUL HAGEDOORN

First of all, this is a well composed document with a thorough consideration of all aspects.

In this document, you outline a model for innovative DPI development and discuss several formulation possibilities, however, I would like to point out that you do not discuss the possibilities for the development of effective DPI's. With an effective DPI you may not need these complex and expensive formulations. Another issue is that, for these complex formulations, you need to incorporate a certain amount of excipient, which increases the total powder volume and some devices do not allow any options for operation on this basis.

In this document, you also mention the importance of the triangle: patient, formulation and devices but we have to balance the forces. We have to balance the adhesive and cohesive forces in the formulation, the separation forces driven by the device but also the deposition forces in the airways. To summarize, we need a DPI that generates effective separation forces and releases the particles with a low velocity in order to avoid inertial impaction, which is responsible for mouth and throat deposition. The internal resistance of the DPI could be very helpful here. The particle velocity decreases as a result of increasing the internal resistance of the DPI. It is misconception that the patient always has to inhale forcefully to create the necessary flow rate. The performance of the DPI depends on the pressure drop generated within the DPI. The flow rate will be the result of the pressure drop and the internal resistance of the DPI. The internal resistance of the DPI determines whether you should inhale forcefully or gently to avoid a high flow rate which leads to high mouth and throat deposition.