

Qualicaps

AN OVERVIEW OF DRY POWDER INHALATION FOR SYSTEMIC DRUG DELIVERY

In this article, Brian Jones, Scientific Advisor to Qualicaps, and Susana Ecenarro Probst, Director of Scientific Business Development, Qualicaps, discuss the growing interest in using inhaled APIs to treat systemic conditions. Furthermore, they review some of the methods used to engineer molecules to be suitable for DPI capsules and look to the possibility of administering biomolecules via the pulmonary route.

Interest is growing in the treatment of systemic diseases using active pharmaceutical ingredients (APIs) administered via inhalation, a method especially applicable to the delivery of biomolecules. Inhalation therapy in its various forms has been used for hundreds of years,¹ used mainly to treat or alleviate conditions of the lungs, asthma and chronic obstructive pulmonary disease (COPD). The advantages of pulmonary delivery over the oral route is that the APIs are not subjected to the enzymes in the gastrointestinal (GI) tract and the effects of first pass metabolism.

Originally, the principal way to avoid the GI tract was by injection or infusion of the API. The latest advancement in API development however, is based on designing biomolecules which cure disease states by interfering with biological pathways in the body. This has changed the challenges of formulation, as the complex structures of these large biomolecules are less stable than the smaller, simpler structures of their predecessors.² It has increased the need for dosage forms that avoid the GI tract and use the other oral route, the pulmonary.

It was reported in 1997 that APIs used to treat asthma will have systemic effects because they are cleared via the systemic circulation,³ thus kindling the interest in this field, which has grown significantly since. By this point, devices for delivery via the pulmonary route had already been developed: nebulisers, metered dose inhalers (MDIs) and dry powder inhalers (DPIs).^{3,4}

The former two use various solvents, both aqueous and organic, thus meaning DPIs offer the best prospect for developing a stable system. Devices for inhalation therapy must be able to aerosolise the formulation so that it is delivered deep into the lungs, where it requires a residence time sufficient for absorption before it is cleared away by the mucus cycle. To successfully arrive at the target location, particles must have both the correct size (1-5 μm) and shape.

EXCIPENTS IN INHALED FORMULATIONS

Treatment of systemic diseases using inhaled APIs is increasing in favour because it can be used with biomolecules: proteins, peptides and the new forms produced by recombinant DNA.^{1,3} The biomolecules that have been studied are shown in Table 1, along with

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Brian E Jones
Scientific Advisor



Susana Ecenarro Probst
Director of Scientific Business Development
T: +34 91 663 08 04
E: secenarro@qualicaps.es

Qualicaps Europe
Avda. Monte Valdelatas, 4
28108 Alcobendas
Madrid
Spain

www.qualicaps.com

their target disease states. Manufacturing protein pharmaceuticals requires processes that will not damage them. For example, spray drying in its various forms has been employed and results in products with a low moisture content, helping to improve their stability.^{4,8} Excipients (e.g. sugars and polyols such as lactose, mannitol and cyclodextrin⁴) need to be added to the formulations to produce particles with the correct aerodynamic properties⁵ and are used to reduce particle aggregation.

An extensive review in 2005 highlighted the advantages of using a carrier based system for delivery: APIs do not innately have the necessary properties and therefore formulations with inert carriers are required for deep lung penetration.³ Carriers have many advantages, enabling more API powder to reach the site of absorption, improving the *in vivo* API stability and improving product taste. The most popular type of inhalation device is the DPI with unit powder doses packaged in either blisters or hard capsules. The efficacy of this method is dependent on the patient's inspiratory flow rate, necessitating the instruction of patients in the correct mode of use.

In 2010 MannKind Corporation made a novel development that introduced a new excipient, fumaryl diketopiperazine (FDKP), a spherical, crystalline particle with a large surface area on which to adsorb the API.⁹ This product was used for Afrezza[®] insulin with a simple breath actuated inhaler. Clinical trials and patient usage showed that Afrezza[®] insulin offered glycaemic control comparable to injected insulin.¹⁰

In 2011 another disease, cystic fibrosis, which had previously been treated with an antibiotic, tobramycin (TP), from a nebuliser, was switched to a DPI with improved results.¹⁰ The formulation was a water in oil micro-emulsion containing perflubron. It was spray dried; as the water evaporates the droplets decrease in size, then the perflubron evaporates to form pores in the particles. This rapid drying process, on the scale of milliseconds, causes the TP to form as an amorphous solid. These particles, called PulmoSphere[®], contain 90-95% TP. The dose is delivered using a breath actuated T-326 Inhaler (Novartis) and powder filled

Disease state	Protein and peptide for treatment
Anaemia	Erythropoietin
Anticoagulant	Heparin
Cancer	LH-RH analogues
Diabetes	Insulin
Diabetes insipidus	1-deaminocysteine-8-D-arginine vasopressin (dDAVP)
Growth deficiency	Human growth hormone
Multiple sclerosis	Interferon- β
Neutropenia	rhG-CSF
Osteoporosis	Calcitonin, Parathyroid hormone
Viral infections	Ribavirin, Interferon- α

Table 1: Proteins and peptides proposed for inhalation delivery, redrawn from "Inhalation delivery of protein therapeutics".⁴

by inhalation grade hypromellose capsules (Qualicaps, Quali-V[®]-I). These were chosen because gelatin capsules become brittle in low relative humidity (RH) storage whereas hypromellose capsules are unaffected by these conditions. Size 3 capsules and the powder fill dose were chosen on the ability of the average paediatric patient (6-10 years) to empty a capsule in a single inhalation.

PARTICLE ENGINEERING FOR INHALATION

Particle engineering was used to improve the stability and aerosol performance of dry powder inhalation for recombinant parathyroid hormone (rPTH).¹¹ The formulation contained a non-reducing sugar, α -trehalose dihydrate (TD) and a non-ionic surfactant (NIS). Mixtures of rPTH, TD and NIS were dissolved in water and the pH adjusted to 7. Particles were formed by either spray drying or spray freeze drying. The particles were assessed using SEM images and tests to measure particle shape, chemical properties and density. Their aerodynamic properties were measured using an Anderson cascade impactor. The powder was filled in a hypromellose capsule and punctured using

a Spinhaler[®] DPI. Results showed that the formulation without NIS was the most stable.

Research was conducted on producing a heat-stable form of oxytocin (OT) aimed at making a particle size of 1-5 μ m.¹² Spray drying, either a standard or low temperature process, was the only way of making amorphous masses using excipients with high glass transition temperatures (GTT), such as lactose, trehalose and citrate salts. The resulting powders were characterised using a variety of techniques to measure their particle size, shape and density. The particles had a median size of 2 μ m and an excellent aerodynamic performance with a respirable fraction up to 70%. The dry powders were amorphous, stable and retained a greater than 90% activity after storage.

A collaboration in 2017 between the University of Parma in Italy and Qualicaps Europe studied the stability of pure spray dried insulin filled into inhalation grade hypromellose capsules (Quali-V[®]-I),⁸ using the commercial insulin product Afrezza[®] for comparison. 2 mg of powder was filled into a Size 3 capsule using a Harro Höfliger Omnidose vacuum drum filler. Capsules were blister packed using transparent PVC/PVDC films for storage trials and samples were then stored for six months at the ICH condition of 25°C, 60% RH (climatic zone II) and fridge conditions of 4°C. Respirability was measured using a Plastiapipe RS01[®] DPI in a new generation impactor. Both formulations showed good emission from the device (>90%). The Parma University formulation showed a significantly high respirability with a fine particle fraction (FPF) of 91.5% and a lower mass median

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aerodynamic diameter. The percentage of degradation products was found to be below USP limits under both storage conditions during the six months of the study. The stability outcome has demonstrated that the formulation contained in the hypromellose capsules (Quali-V®-I) together with a PVC-PVDC blister packaging material can offer a stable therapy less dependent on cold chain storage.

DELIVERING BIOMOLECULES VIA INHALATION: PROSPECTS & CHALLENGES

The use of the pulmonary route for delivering proteins and peptides is a viable proposition, the challenges and perspectives being discussed in a review paper in 2013.¹⁴ Three available delivery devices were analysed: nebulisers, MDIs and DPIs, with the fact that only DPIs did not use liquid formulations being highlighted. The particle size and shape requirements for dry powders were related to the anatomical features of the lungs. The use of DPIs relies on the patients' inspiratory efforts to provide the energy to disperse the powder particles, which involves fluidisation, then de-agglomeration

to form a fine, respirable aerosol cloud. DPIs have design features to aid this process.

The formulated powders must maintain the integrity of the protein and avoid degradation during processing and storage. The formulation and manufacturing processes are related to potential problems. The excipients used to stabilise formulations and their regulatory status were explained, being used to modify lung clearance mechanisms and improve systemic bioavailability. Absorption mechanisms have different pathways related to API molecular mass. The regulatory status of applications for approvals were listed with their safety aspects. The history of marketed inhaled insulin products was discussed, particularly the problems surrounding Exubera® insulin (Nektar, Pfizer) and its subsequent withdrawal from the market after one year due to unexpectedly low sales, most notably its cumbersome and difficult to use inhaler.

Another, more recent paper summarised the challenges and prospects for the delivery of biologicals.¹⁵ Three routes were given, oral mucosal, pulmonary and transdermal with details of the product formulation requirements. For pulmonary development,

the product pipelines have shifted from a mix of small molecules to biologics, a significant shift from when low cost asthma and COPD APIs were the market targets. The key factor for inhalation and deep penetration into the lungs is the aerodynamic particle size of the formulation. Only particles with aerodynamic diameters of less than 3 µm will reach deep into the lungs and be absorbed into the blood stream to treat systemic diseases. Progress requires a combination of particle engineering and device design to achieve this goal. Currently over 30 APIs are at various stages in the development process, either in preclinical testing or in Phase I and II trials.

ABOUT THE COMPANY

Qualicaps, a wholly owned subsidiary of Mitsubishi Chemical Holding Corporation, has over a century of experience in manufacturing hard capsules and a strong record of pioneering in new forms of drug administration. Qualicaps is responsible for several milestones in the history of two-piece hard capsule development, having introduced features so widely accepted and trusted that they have since become industry standards.

As a company dedicated to capsules, Qualicaps has a unique perspective on how to contribute to health, delivering pharmaceutical-grade capsules together with a comprehensive service along the drug product lifecycle, through a global team of commercial, scientific and technical services. Geared toward quality and functionality, they deliver on being “Engineered to perform” by offering not only exceptional performance from their capsules, but also from their team, made up of subject matter experts who partner with customers on optimising dosage form development and operational effectiveness in encapsulation during drug product manufacturing.

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ABOUT THE AUTHORS

Brian Jones has extensive experience in the field of hard capsules, both in their manufacture and usage. He has visited pharmaceutical companies in the US, Europe, Africa and Asia to give lectures and to assist in problem solving for this particular dosage form. He has been involved with hard capsules and their use and performance in dry powder inhalers since their introduction to the market in the 1960s. Mr Jones has Bachelor's and Master's degrees in Pharmacy from the University of Wales and is a Fellow of the Royal Pharmaceutical Society of Great Britain. He is an honorary senior lecturer in the Welsh School of Pharmacy and Pharmaceutical Sciences, Cardiff University, UK.

Susana Ecenarro Probst supports R&D centres within the pharmaceutical industry in new drug developments by providing scientific and technical expertise, as well as promoting collaborations with European universities and third parties that focus on the application of state-of-the-art capsule technologies. Prior to Qualicaps, she worked for Schering AG for 18 years, working in diverse QA positions and covering several functions, including analytical development, process validations, technology transfer, and operational excellence projects, amongst others, followed by five years of experience leading an analytical R&D unit of a Bayer Healthcare facility. Ms Ecenarro Probst holds a MBA and a Bachelor's degree in Pharmacy.

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