PEER REVIEWED

Local Lung Delivery for Small and Large Molecules Via Dry Powder Inhaler

Inhalation is a familiar route of delivery for many drugs designed to treat asthma and related conditions. Asthmatics routinely carry some form of metered dose inhaler around with them to relieve the symptoms of attacks, and many take preventative medicines such as steroids via inhalers, too. Nebulisers are also used to deliver asthma medications directly to the lungs, often for those who find using a metered dose inhaler difficult (such as children and the elderly).

The growing incidence of chronic obstructive pulmonary disorders (COPD) has led to a rise in drug treatments for respiratory conditions being delivered by inhalation, but other lung diseases also benefit from direct delivery to the lungs. Mannitol, for example, can be given in a dry powder inhaler (Chiesi's Bronchitol) to help cystic fibrosis patients clear mucus from their lungs. And for pulmonary arterial hypertension iloprost (Ventavis, Janssen) can be delivered directly to the lungs with using a mesh nebuliser. This greatly aids its efficacy, as the drug only has a half-life of about half an hour; multiple doses are required every day, and newer nebuliser types have since helped reduce the treatment burden.

Delivering treatments for lung diseases by inhalation is an obvious choice, as there are significant advantages when diseased tissue or an infection is within the lung itself. Pulmonary administration also circumvents first pass metabolism in the liver. On account of the high surface area of the lung, the onset of action can be faster, as is clearly the case for beta-agonists such as salbutamol/albuterol when treating acute exacerbations of asthma.

However, small molecule APIs such as these are not the only drugs used to treat lung disease. Monoclonal antibodies (mAbs) and other proteins, peptides and oligonucleotides have all been investigated as both systemic and local treatments for lung diseases. For example, at least five FDA-approved mAb treatments are available for asthma today, all of which are administered by injection. In 2022, a mAb was approved in the EU for the prophylactic prevention of respiratory syncytial virus (RSV) in children. And during the Covid-19 pandemic, mAb treatments were approved in the EU and the US for severe cases of the disease. Some of these combined more than one agent in the same treatment.

As with small molecule APIs, there can be significant advantages in delivering biotherapeutics locally to the lung, including tissue-specific targeting, which can improve side-effect profiles. There are significant manufacturing challenges involved in formulating sensitive biotherapeutics as dry powder for inclusion in an inhaler device, and most investigations into inhaled delivery of biologics rely on devices such as mesh nebulisers. Yet DPIs are much preferred by patients and caregivers because of their ease of use, portability, and shelf stability.

Spray-dried Biologics

However, while there remain challenges, it is possible to formulate antibodies and other biotherapeutics as stable dry powders via a carefully designed spray drying process. In spray drying, the API and the excipients are dissolved together in a volatile solvent; this will be water or a buffer for most biotherapeutics. The solution is passed through an atomiser which breaks it up into small droplets, and then sprayed into a drying chamber.

As the droplets encounter a heated drying gas within the chamber, they dry rapidly and form solid, engineered particles whose size distribution is tightly controlled. For direct delivery to the lung, the particles will be engineered to have aerodynamic diameters of about 1–5µm, which is the most appropriate size for pulmonary delivery.

Biotherapeutic molecules need to be handled carefully, as many are sensitive to thermal, shear and dehydration stresses. Instinctively, this makes spray drying appear to be a risky process that might damage or destroy the molecules. Steps are taken in both the process and the formulation to ameliorate these risks. Protective excipients, including sugars such as trehalose, can help to stabilise the delicate molecules as they dry. Furthermore, the evaporative cooling that occurs in the liquid droplets reduces the exposure of the material to high temperatures during the drying process. Several recent review articles outline progress in pulmonary delivery of spray dried biotherapeutics; the references are listed below.

Cancer Treatment Via Inhalation

A recent case study using the anticancer agent bevacizumab highlights the potential of spray drying a mAb to facilitate the local treatment of lung cancer. The vascular endothelial growth factor (VEGF) inhibitor is approved for the treatment of various forms of cancer, including non-small cell lung cancer (NSCLC), and works by inhibiting angiogenesis, reducing the ability of the tumour to create new blood vessels.

In NSCLC, it is given by intravenous infusion in combination with chemotherapy in three-week cycles. However, the risk of unexpected bleeding prevents many of the patients who might benefit being treated with the antibody. If it were delivered locally to the lungs rather than dosed systemically, the exposure of healthy tissue would be much lower, likely cutting the chances of these adverse events. Likely, it would also improve patient compliance, as it could be administered in a home setting. In addition, the need for cold chain storage would also likely be eliminated.

When embarking on the development of a formulation for a DPI, it was important that the biological activity of the antibody was preserved; this could be assessed using a cell-based assay. The powder needed to have the correct aerosol properties for delivery to the deep lung. It also, ideally, needed to have good physical stability at 25°C.

The answer lay in the careful selection of excipients. The non-reducing sugar trehalose, commonly used to stabilise proteins in both liquid and solid formulations, was one component. The other, the amino acid L-leucine, is commonly used in formulations for inhalation to improve powder dispersibility. Initial studies indicated that a spray-dried powder that was 40% bevacizumab by weight, 40% trehalose and 20% leucine, the highest loading evaluated, met all the requirements for key performance attributes.

Fortunately, the activity of the spray dried powder against VEGF remained comparable to the as-received antibody. Furthermore, there were no traces of fragmentation or aggregation of the protein in size exclusion chromatography and dynamic light scattering experiments. And, importantly, a solution of the powder in phosphate buffer remained optically transparent.

The powder's aerosol properties were also tested. With a fine particle fraction of 81%, and a mass median aerodynamic diameter of 2.2µm, the particles fell well within the required specifications for delivery to the deep lung. An ICH stability study where it was packaged with desiccant and stored for a year at both 5°C and 25°C showed that the only noticeable change was a small increase in the powder's water content. All its other aerosol and physical properties remained the same at both temperatures, as did its bioactivity.

The next step was in vivo testing in a rat model of NSCLC, carried out in conjunction with Lovelace Biomedical. Rats were given weekly treatments, and the lung weight at 12 weeks was determined as a measure of the tumour burden. Three different drug regimens were included in the study: injected bevacizumab plus cisplatin (standard of care), inhaled bevacizumab both alone and in conjunction with injected cisplatin, plus an untreated group acting as a negative control. The inhaled dose was a tenth of the size of the injected dose.

All three different regimens gave a significant reduction in tumour burden when compared to the untreated group. Importantly, the inhaled mAb in conjunction with cisplatin was as good at reducing the tumour burden as the regimen where both were injected, despite the 10-fold reduction in antibody dose. Even when administered alone, the inhaled bevacizumab reduced the tumour burden, albeit by a smaller amount than when it was given with cisplatin. This combination of efficacy and stability indicate that the formulation may have huge potential in treating patients with NSCLC in a less burdensome way.

Combination Inhaled Treatments

It would be even less burdensome if the other elements of a complex NSCLC treatment regimen could also be delivered via inhalation. Chemotherapy, other receptor-targeting drugs, and immunotherapies are all commonly administered alongside bevacizumab. Might it be possible to include more than one drug in the same inhaler?

We therefore looked at whether it would be possible to create an inhaled formulation that comprised bevacizumab plus one of the chemotherapies cisplatin and paclitaxel, or the EGFR inhibitor erlotinib. Unsurprisingly, this posed a significant manufacturing challenge – small molecule drugs would commonly simply be micronised to create the powders, but this is not appropriate for a protein drug. Again, the answer lay in spray drying.

This posed a real challenge. Bevacizumab must remain in an aqueous solution to preserve its activity, but the solubility of both paclitaxel and erlotinib in water is poor. Cisplatin is a little more soluble in water, but its chemical stability in aqueous solution is poor. Add in the excipients, and it was simply impossible to imagine an appropriate solvent that is suitable for all the components.

Instead, we turned to simultaneous spray drying. In a simul-spray process, two separate solutions are spray dried into dry powders in the same spray dryer at the same time via separate atomisers. The two different powders form an intimate mixture in the collection container, ready for further testing and formulation. A scanning electron microscope image of the mixture can be seen in Figure 1.

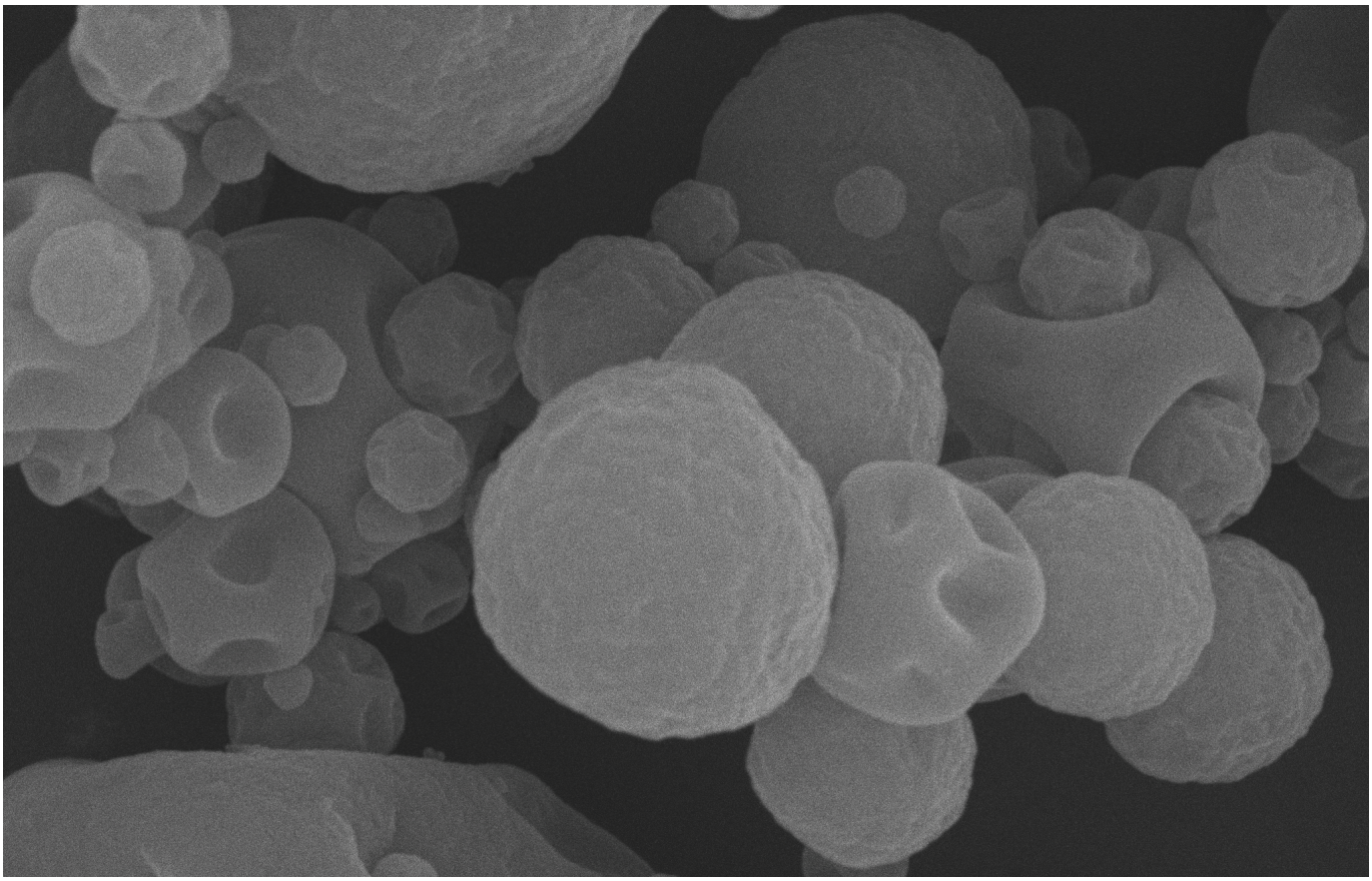


Figure 1: Scanning electron microscope image of simul-spray cisplatin and bevacizumab powders. Bevacizumab particles have a smooth surface with a collapsed sphere shape, and cisplatin particles have a rough surface and nearly spherical shape.

The first step of testing involved making individual dry powder formulations of each of the drugs. That for bevacizumab was the same as had been used in the single agent powder study. Paclitaxel and erlotinib included leucine to improve dispersibility, and as well as leucine, trehalose was included in the cisplatin powder to improve its stability.

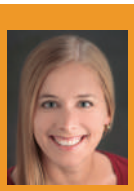
Combination formulations of bevacizumab plus each of the three other drugs were then created, in several different ratios. Scanning electron microscope images of both the single API formulations and the simul-spray combinations showed that they were uniformly blended powders, with the two different types of particles distinguishable by eye. The drug concentration in the powders was also assessed.

Activity could not be assessed in a cell-based assay because of the cytotoxic nature of both paclitaxel and cisplatin. Instead, the formulations were reconstituted, incubated with VEGF, and then the amount of unbound VEGF measured via ELISA. It remained similar to non-spray-dried bevacizumab in all cases. The aerosol properties were then also checked, with the particle size distributions of the two types of particle being similar in each different combination. Median aerodynamic diameters fell in the range 1.8–2.9µm, again suitable for inhaled delivery to the deep lung.

The Outlook

Elsewhere, there are other positive signs. The commercial approvals of two inhaled insulin formulations, in 2006 (Exubera) and 2014 (Afrezza), paved the way for future work. Two antibody-based drugs formulated as DPIs have already completed Phase 1 clinical trials, both in asthma: abrezekimab, an anti-IL13 antibody fragment from UCB/Vectura, and ecleralimab, an anti-thymic stromal lymphopoietin (TSLP) antigen binding antibody fragment from Novartis. Both included trehalose as a stabilising excipient. Phase 2 studies in both uncontrolled asthma and COPD have also begun for ecleralimab.

It remains early days for the inhaled delivery of monoclonal antibodies via dry powder inhaler as none have yet reached the market. But the signs are looking promising. In the coming years, patients may well be able to benefit from the local delivery of biologic drugs for lung diseases via a convenient dry powder inhaler device.



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