

Inhaled products of the modern era: drugs for non-respiratory conditions

In this first article in a series that will look at developments in new drug technologies, **Jenny Bryan** describes the development of products for pulmonary delivery including formulations of insulin, analgesics and drugs for erectile dysfunction

The alveoli are an inviting target for pharmaceutical companies developing products which cannot be administered orally

With a surface area of 100 square metres, it is not hard to see why the alveoli of the lungs are such an inviting target for pharmaceutical companies intent on developing fast acting peptide and other products which cannot be administered orally. But it has taken 80 years for Exubera — the first inhaled formulation of insulin — to come within sight of the winning post. Currently under scrutiny at the European Medicines Evaluation Agency, Exubera will also be the first inhaled product of the modern era to reach the market for a condition that does not affect the respiratory system.

Lining up behind are rival insulin inhalers, impotence treatments, hormones and analgesics. But, for each, it is a long and arduous journey. For asthma and chronic obstructive airways disease, it may be enough for a metered dose inhaler to get as little as 20 per cent of the drug dose into the deep lung. But to get enough drug into the alveoli for viable systemic absorption has required a rethink of the characteristics needed both for drug particles and for delivery devices.

Where it all began

Ironically, however, it was the need to replace chlorofluorocarbons (CFCs) as propellants in respiratory inhalers which breathed new life into pulmonary delivery, and the research

which followed is at last bringing products for systemic diseases, such as diabetes, to market.

“In the 1980s, people were working on hydrofluoroalkanes (HFAs) as replacements for CFCs, but there were concerns that, if HFAs did not work well enough, other systems would be needed. At the same time, biological products were starting to make inroads, and everyone was looking for new ways to deliver proteins,” says Andy Clark, chief scientist at Nektar Therapeutics, the company which developed the inhalers and insulin formulation for Exubera. The result is a new generation of dry powder devices, designed to fulfil different requirements to inhalers for lung diseases.

Chris Blackwell, chief executive of UK-based pulmonary product development company, Vectura, explains that the key requirement is to get small particles, smaller than 5µm and preferably smaller than 3µm, into the deep lung. Once there, it is equally important to ensure that active drug deaggregates easily from its carriers, for fast absorption from the alveoli into the circulation.

Devices like Vectura’s Aspirair get up to 70 per cent of the fine particle dose into the

alveoli, compared with the 35 to 40 per cent achieved with conventional dry powder devices for respiratory diseases. Earlier attempts at intranasal insulin delivery fell by the wayside because it proved impossible to get enough drug through the nasal mucosa without adding permeation enhancers that made patients’ noses sore. In contrast, by getting 60 to 80 per cent of the insulin dose into the alveoli, Nektar is achieving absorption levels into the circulation of about 15 per cent with Exubera — sufficient to keep blood glucose levels within accepted parameters.

Comparable with insulin by injection

Latest results with Exubera for treatment periods up to four years, show that type 1 and type 2 diabetes patients maintain glycaemic control comparable with that achieved with insulin injections. Equally important, Exubera — which will be marketed by Pfizer and Aventis — does not cause any clinically important changes in pulmonary function.

As Dr Clark points out: “When you take a drug to the regulators that you’re putting into the lungs for systemic treatment, you’ve got to be very sure that you aren’t doing any damage to the lungs.”

While Exubera is a dry powder formulation, delivered from an inhaler about the size of a household torch, Novo Nordisk’s



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inhaled insulin, NN1998, is a liquid formulation which uses the AERx inhaler developed by the California-based company, Aradigm. Using a liquid makes it possible to adjust the dose of insulin to the nearest unit — just as with injections — something that does not appear to be possible with powders.

However, NN1998 hit a setback earlier this year when Novo Nordisk ended a 24-month phase III safety and efficacy study early because it became clear that post-prandial glucose suppression was being delayed in the type 1 diabetes patients in the trial. This meant that post-prandial glucose levels were higher and night-time levels lower than in a comparator group using subcutaneous insulin. Previous phase II studies in type 2 diabetes had not shown the same problem.

Both Exubera and NN1998 have been developed for mealtime glucose administration, since companies have not yet found a way to prolong pulmonary insulin absorption for baseline glucose control.

“The current formulations are fast acting but they come out quickly too. So people with type 1 diabetes will still need to inject to control their baseline glucose,” explains Dr Clark. “We’re now trying to formulate the insulin to slow things down, for example, by attaching polyethylene glycols,” he adds.

Analgesics

Pain control is another area where there has been considerable interest in pulmonary delivery, and Nektar is looking at the potential

for novel migraine treatments. Aradigm is using its AERx system for morphine inhalation in acute and breakthrough pain control. It recently reported results of a placebo controlled trial of multiple doses of inhaled morphine, intravenous morphine or placebo in 89 patients following bunion removal. There was similar efficacy in onset of pain relief between the inhaled and intravenous delivery methods and superior efficacy to placebo.

But, again, there is the challenge of controlled release from the lungs so that analgesia is prolonged beyond acute relief.

Erectile dysfunction

Although Vectura believes that Aspirair has the potential to deliver peptides and other macromolecules, it is currently focusing its research on pulmonary delivery of small molecules. In addition to respiratory products, it is developing inhaled dry powder apomorphine hydrochloride (VR004) for the treatment of erectile dysfunction (ED).

A recent small dose response study showed that VR004 was rapidly absorbed from the lung, with maximum plasma concentrations one to three minutes after dosing. Elimination of drug from plasma was relatively rapid, with a terminal half-life of approximately 60 minutes.

In a previous study, an improvement in erectile performance was achieved in 59 per cent of 35 patients with mild to moderate ED. The median onset of response was eight minutes, with some subjects responding three minutes after dosing. Further phase II

studies are planned for the end of 2004/early 2005.

Another apomorphine-based inhaler product, VR400, is ready to go into phase II studies for the treatment of female sexual dysfunction, but Dr Blackwell explains that the company is likely to wait for a marketing partner for VR004, before proceeding further with VR400. In contrast, the company is eager to start phase I studies with its third systemic product for pulmonary delivery. This is VR776, an as yet unidentified, off-patent neuroactive drug for the treatment of premature ejaculation. “There are three times as many men with premature ejaculation as with ED, and there are no approved treatments on the market to help them. There is a tablet version of the product we are developing, but it takes about two hours to work. We are reformulating it to work much more quickly by inhalation,” says Dr Blackwell.

Time to see products benefit patients

Although inhalation products like VR776 will inevitably steal the headlines, it is the income from refinements in delivery devices for asthma and chronic obstructive pulmonary disease which will fund future developments at companies like Vectura, Nektar and Aradigm into novel treatments for non-respiratory conditions. Because, as Dr Clark points out: “The 90s were a pretty wild decade for new technologies and potential applications for pulmonary delivery. It’s about time we got some of the products onto the market where they can benefit patients.”