Inhaling medicines: delivering drugs to the body through the lungs

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Abstract | Remarkably, with the exception of anaesthetic gases, the ancient human practice of inhaling substances into the lungs for systemic effect has only just begun to be adopted by modern medicine. Treatment of asthma by inhaled drugs began in earnest in the 1950s, and now such 'topical' or targeted treatment with inhaled drugs is considered for treating many other lung diseases. More recently, major advances have led to increasing interest in systemic delivery of drugs by inhalation. Small molecules can be delivered with very rapid action, low metabolism and high bioavailability; and macromolecules can be delivered without injections, as highlighted by the recent approval of the first inhaled insulin product. Here, we review these advances, and discuss aspects of lung physiology and formulation composition that influence the systemic delivery of inhaled therapeutics.

In 1986, researchers at Genentech discovered that human growth hormone (hGH), a 192-amino-acid protein (~22 kDa), was naturally absorbed into the systemic circulation of rats following instillation into the lungs[1]. Until then, and to some extent for the following 20 years until the recent approval of the first inhaled insulin, non-invasive delivery of proteins has been a 'Holy Grail' among drug delivery scientists. All other non-injection routes of delivery (including oral, buccal, transdermal and nasal) were shown to be virtually impenetrable to macromolecules unless penetration enhancers were used. Typical enhancers act like detergents that break down (solubilize) cell barriers, yielding good bioavailabilities but also raising long-term safety issues[2]. All of the enhancer-based delivery programmes initiated in the 1970s and 1980s with nasal insulin and nasal hGH were eventually terminated, some after extensive human trials[3–5]. A number of different penetration enhancers are under development that might work by different mechanisms than those described above (for example, transient cell-junction opening), but their regulatory approval could be some way in the future.

The findings with hGH were not the first to demonstrate that the lungs were naturally permeable to peptides (TABLE 1). In 1925, Gänsslen showed that inhaled insulin, a 51-amino-acid peptide (5.7 kDa), lowered blood glucose in all five diabetic subjects tested[6] and other reports over the years confirmed these initial findings[5]. The reasons why it took nearly 80 years to capitalize on the fact that nature had left a door open for macromolecule entry into the body are uncertain. However, the half-page Gänsslen paper was in German and only 'rediscovered' in the 1970s, when the doomed nasal programmes still looked promising. Additionally, pulmonary delivery seemed to be impractical, complicated, inefficient and unreliable, and its long-term safety was unknown. Things have changed dramatically — the development of inhaled insulin began in 1990 at a start-up company, Inhale (now Nektar), and is now being continued by a variety of companies[7]. Today there are several inhaled insulins in development that are as reliable as, or more reliable than, injections, and the growing long-term safety database is reassuring[7–10]. The furthest in development of these formulations is inhaled human insulin powder of recombinant DNA origin (Exubera; Pfizer), investigated in a large number of adult patients with type 1 or type 2 diabetes, and recently approved in Europe and the US for the treatment of adults with diabetes. An ancient delivery route is therefore now being exploited in ways never imagined. Insulin leads the way and other peptides and proteins, including some of the most exciting new therapeutics, might now have an entry route into the body that does not require needle-based injection.

Inhalation also offers great potential for rapid (within seconds or minutes) systemic delivery of small-molecule therapeutics. Because of the huge surface area of the lungs, the highly dispersed nature of an aerosol, (hundreds of millions of particles per dose), good epithelial permeability and small aqueous volume at the absorptive surface[11], small molecules deposited in the lungs are very rapidly absorbed into the systemic circulation,

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