A New Technology for Pulmonary Drug Delivery

Ying Ma, Chemical and Biochemical Engineering, The University of Western Ontario, 476, Thomson Engineering Bldg., London, ON N6A5B9, Canada
Jesse Zhu, Chemical & Biochemical Engineering, The University of Western Ontario, 476, Thomson Engineering Bldg., London, ON N6A5B9, Canada.

Introduction

Pulmonary drug delivery is a much more effective and efficient method than taking drugs through the digestive system, and a much more convenient and safer method than injecting drugs intravenously. Human lung has a surface area of 80m^2 and delivering drug through the lung can short-cut the digestive system so that only a small fraction of the normal drug dose is required for the same treatment. It is very effective for treatment of respiratory diseases such as asthma and tuberculosis, and also good for mucosal vaccination and other systemic delivery of drugs such as insulin and anti-infectives. To deliver the drugs directly into human lungs, however, their size must be smaller than 5 microns. The handling of these ultrafine drug powders presents a serious problem during packaging and administration since they agglomerate badly. Current methods are (1) to blend them with a large amount of coarser excipient powders to make them flow better or (2) to suspend them in liquid. While both methods overcome the inter-particle forces during packaging, they cause other problems such as giving too large a dose for inhalation and restricting the actual delivery efficiency into the lung to about 20% at most. In the first method, a large amount of ultrafine powders stay with the coarse excipient, which lands in the mouth. In the second, ultrafine powders tend to be pushed against the back of the mouth by the high-velocity spraying liquid.

Our approach is to utilize our new ultrafine powder handling technology to meter and deliver the drugs, so that these ultrafine drugs can be used alone, without the "aids" of coarse powder or liquid (excipients). The first key achievement of the new technology is the ability to accurately dispense a tiny quantity (in the order of 0.02 to 0.5 milligrams per dose) of the ultrafine drugs (< 5 microns). The second key achievement is the development of a more effective inhaler that gives much higher delivery efficiency (> 50%) than those currently on the market. This research project, with several patents granted, has produced a combination of new drug handling processes and new inhalers that are likely to eventually set an industry standard for pulmonary drug delivery in the near future.

Novel Technology

A rotating fluidized bed powder dispensing device (Figure 1) was developed to dispense the extrafine drug particles into a novel dry powder inhaler (DPI) (Figure 2). Tests were carried out with various 1-5 micron powders such as salbutamol sulphate, insulin, lactose, and mannitol. The dispensing device is designed to permit filling of up to 60 doses per minute, with weights ranging from 20 micrograms - 2000 micrograms metered into a multi-dose blister pack, integrated into the DPI.

The patented rotating fluidized bed powder dispensing device has a rotating porous cylindrical chamber with alternating distributor and ceiling, and a flexible nozzle for additional agitation. It is designed to prevent the agglomeration of extrafine particles in the absence of any large excipient particles. With such an arrangement, the extrafine particles can be fluidized inside the chamber to produce a uniform gas-particle suspension which can be withdrawn from the fluidized chamber as a gas-particle plume. At the withdrawal port, up to 60 doses per minute (20 to 2000 micrograms) can be metered into a multi-dose blister pack.

The breath-activated, excipient-free dry powder inhaler (Figure 2) was designed to facilitate delivery of drug powders deep into human lungs. The Andersen Cascade Impactor, Next

Generation Impactor and TSI particle size distribution analyzer were used to evaluate the performance of the DPI in conjunction with salbutamol sulphate, insulin, lactose and mannitol.

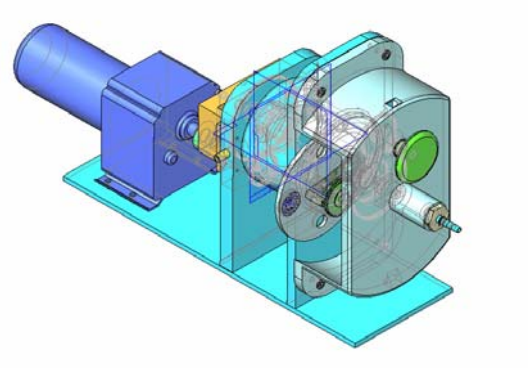

Figure 1 Fluidized bed dispensing device

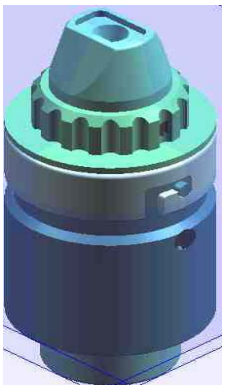

Figure 2 Dry Powder Inhaler

Results

Testing revealed that the rotating fluidized bed powder dispensing device can provide a dilute gas-solid suspension with more than 90% of the particles present in discrete (non-aggregated) suspended form. For example, results show that the majority of insulin particles in the plume exiting the fluidized dispensing device are under 3 micrometer with a narrow particle size distribution and only one peak. The particle size distributions in the plume measured by TSI particle size analyzer clearly indicates that the starting powder can be broken into single particles effectively through the fluidized bed powder dispensing device (shown in Figure 3). The dose uniformity of each powder filled by the dispensing device was tested using disks with different dosage sizes (20 - 2000 micrograms). The deviations among the doses in the same disk and between the disks under the same condition were very small - the relative standard deviation (within the disk) of the filled weights into the different size dosage disk was less than 5% (shown in Figure 4).

The new inhaler was also found to be very effective, much more than those currently on the market. *In-vitro* tests have shown that the newly designed DPI exhibits a high fine particle fraction (< 4.7 microns) of approximately 60%-80%, using both Andersen Cascade Impactor and Next Generation Impactor (Figure 5).

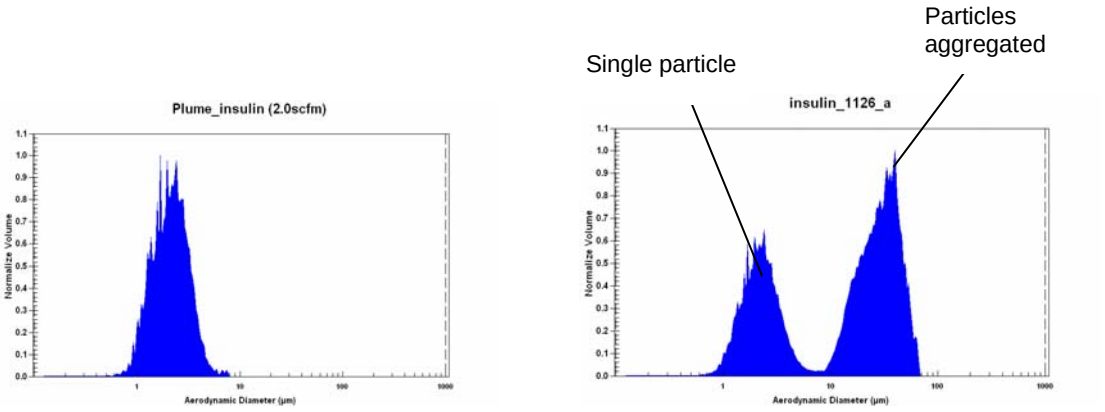

Figure 3 Particle Size Distribution of the Insulin Powder by TSI Particle Size Distribution Analyzer (Left: Gas-solids plume flow out of the dispenser; Right: Bulk powder)

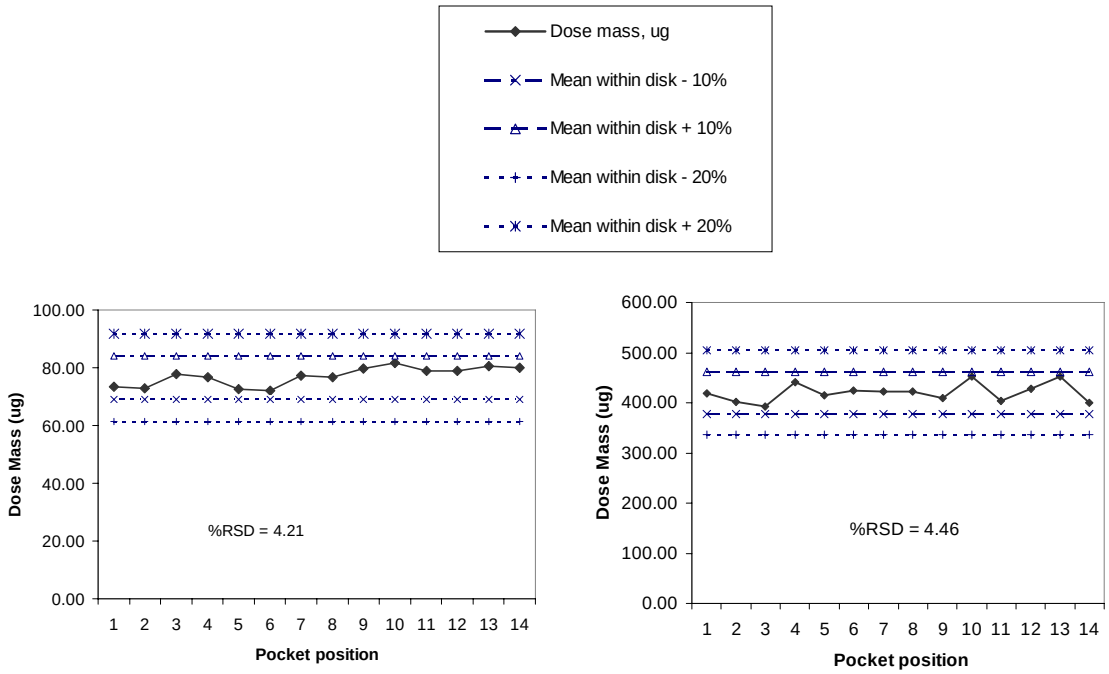

Figure 4 Uniformity test for dispensing device using spray dried insulin powder (2.10μm) within different size disks

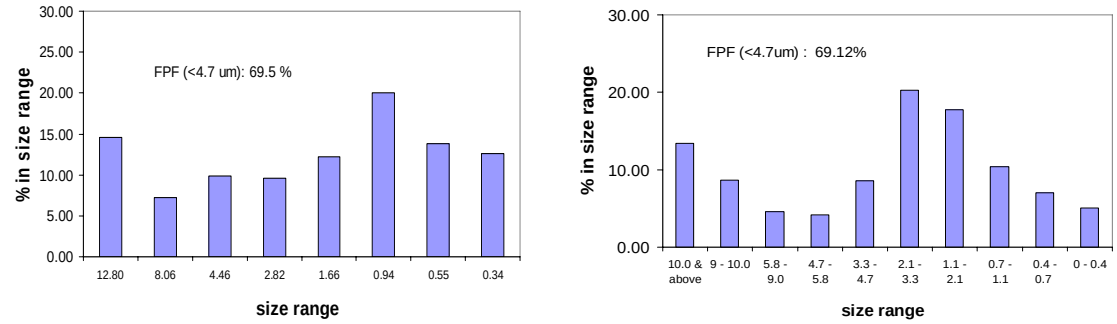

Figure 5 Aerodynamic particle size distribution of spray dried insulin powder (2.10μm) delivered via new DPI Using Andersen cascade impactor (left) and Next Generation Inpactor (right)

Conclusions

The combination of the new breath-activated and excipient-free dry powder inhaler and the rotating fluidized bed powder dispensing device can efficiently dispense and deliver extremely small quantities (as low as 20 micrograms) of extrafine drug particles with the RSD below 5%. Approximately 60%- 80% of fine drug powder can be delivered into human deep lung via new designed dry powder inhaler.