CASE STUDY

UniDose: The development of a novel aerosol collection apparatus for dissolution testing of orally inhaled drug products

The case study highlights the concerns with current aerosol collection systems for dissolution studies of OIDPs and the development of Nanopharm's UniDose apparatus as a robust method for collection and discriminating the dissolution properties of the aerosolized dose of inhalable formulations.

Keywords: Formulation, Dissolution, Aerosol collection, IVIVC, quality control

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Background Information

Inhaled biopharmaceutics and the necessary in vitro tools required for predicting clinically relevant endpoints of safety and efficacy have become critically significant in the development of bioequivalent OINDP products.

Recent pharmacokinetic (PK) studies have suggested that successful in vitro based equivalence of the aerodynamic particle size distribution may not directly ensure in vivo equivalence in pulmonary absorption, safety profiles and therapeutic efficacy of the test product.

The lung bioavailability of an inhaled drug depends on the site of deposition and the physicochemical properties of the drug formulation. Drug particles that deposit in the peripheral, non-ciliated regions of the respiratory tract must undergo dissolution before metabolism or transport across the lung membrane can occur.

Dissolution is therefore a prerequisite for cellular uptake and/or absorption via the lungs. For low soluble APIs, simulations suggest dissolution rate is the main driver for drug retention in the lung. There is, however, no pharmacopeial method to determine the in vitro dissolution rate of aerosols generated by inhaled products. This lack of a universally accepted method for estimating the dissolution behaviour of OIDPS presents an obstacle to the successful development of reliably bioequivalent formulations and products.

A reliable means of measuring the dissolution behaviour of inhaled products may have a number of applications. It could be applied in the context of quality control as a tool for evaluating material properties, and processing effects on the active ingredient dissolution. It would be of general application in collection and dissolution studies of the aerosolised dose. The most important potential application would be to provide an *in vitro-in vivo* correlation (IVIVC) based technique for OIDPs.

What are the major challenges?

In any dissolution method, the two key steps are the collection of the inhalable dose to be dissolved and the dissolution step of dissolving the collected dose.

Studies have indicated good correlation between in vivo based measurements of total lung deposition and in vitro measurement of lung dose. There is therefore a need to collect a representative total lung dose for dissolution studies (e.g. ex-cast dose, impactor stage mass or a dose below a defined impactor stage etc.).

Furthermore, the dissolution characteristics ought to be independent of the method of collection and the loaded dose. As shown in Figure 1, the absence of consistency in the dissolution rate measurements with current systems is thought to be directly attributable to an artefact of the collection process itself.

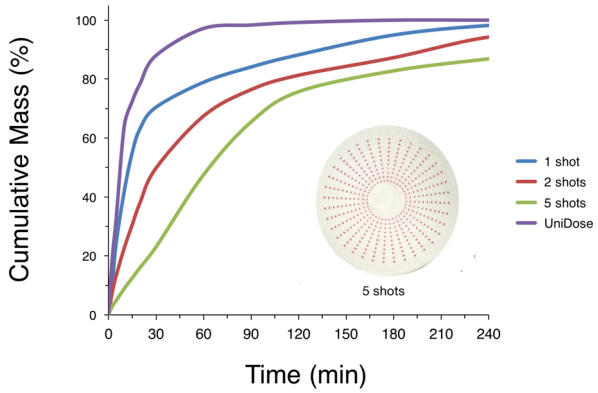

Figure 1: Dissolution release profiles of fluticasone propionate from a current collection system with increasing drug loading and direct comparison with the UniDose system.

The significant variation observed in dissolution behaviour with the use of current collection systems has limited the sensitivity required in the dissolution data, This has created major challenges when comparing formulations with differing fine particle mass of the same product.

UniDose: A dose independent aerosol collection apparatus

To overcome the limitations of current collection systems, Nanopharm has developed a proprietary aerosol dose collection system for the dissolution testing of OIDPs.

The UniDose apparatus uniformly deposits the whole lung dose (e.g. ex-cast dose, impactor stage mass etc.) directly onto a single, high surface area filter membrane under laminar flow and low impaction velocity.

The drug loaded filters can be subsequently used for dissolution studies with a standardized dissolution test apparatus such as Franz cell, USP IV flow through, USP V Paddle over Disk apparatus etc..

The uniformity of deposition on the filters of the UniDose is illustrated in the Figure 1, upon actuating 1, 2, 5 and 10 of a red ink dye, which has been formulated as a solution MDI.

This uniform dosing leads to independence of drug loading on the dissolution characteristics as demonstrated in the dissolution plots of fluticasone propionate in Figures 2A and B, of a DPI and suspension based MDI formulation after 1, 2, 5 and 10 actuations, respectively.

The UniDose has overcome the severe limitations of current collection systems and has enabled greater ruggedness, reliability and increased the discriminatory capability in determining dissolution differences of deposited aerosols, which is less susceptible to variation in accordance with the amount of material deposited on the filter.

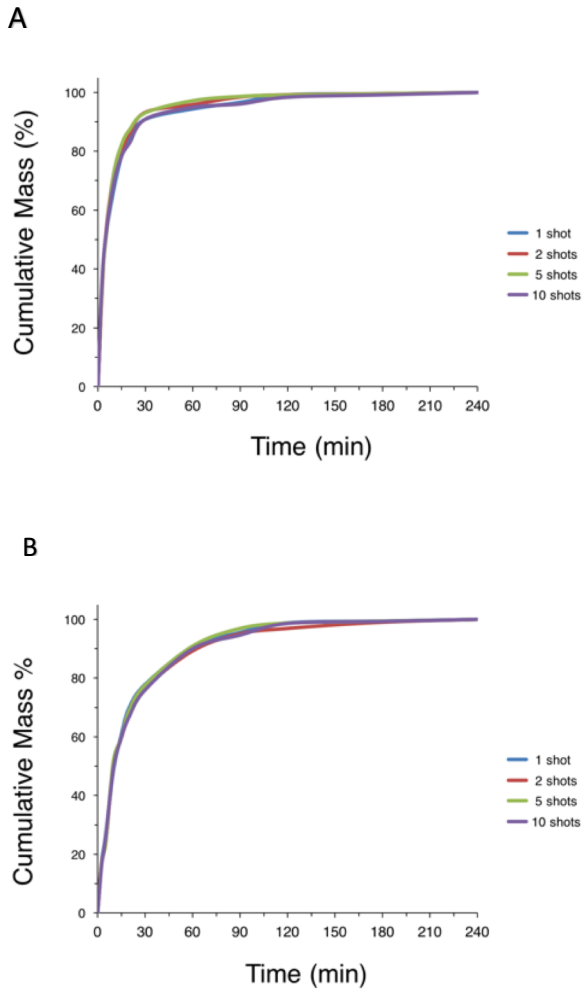

Figure 2: Dissolution release profiles of an in-vitro lung dose (impactor stage mass) of fluticasone propionate with increasing drug loading of (A) 1, 2, 5 and 10 actuations of Flixotide DPI Accuhaler and (B) 1, 2, 5 and 10 actuations of a Flixotide MDI Evohaler.

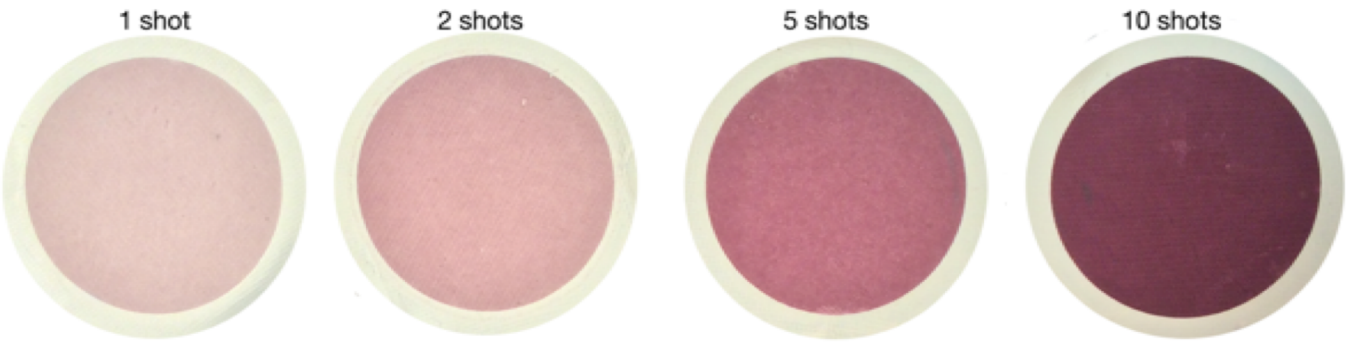

Figure 1: UniDose - Uniform dosing with increasing number of doses as illustrated by the aerosol deposition of a red dye formulated as a solution based MDI