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Dissolution of fine particle fraction from truncated Anderson cascade impactor with an enhancer cell

Justin Yong Soon Tay, Celine Valeria Liew, Paul Wan Sia Heng*

GEA-NUS Pharmaceutical Processing Research Laboratory, Department of Pharmacy, National University of Singapore, 18 Science Drive 4, Singapore 117543, Singapore

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ABSTRACT

Dissolution testing for inhalers were previously conducted either on unfractionated drug-carrier powders or drug of specific aerodynamic particle size. In this study, the collection of the full fine particle fraction (FPF) was attempted on a single stage. Capsules containing 30 mg of 2% salbutamol sulfate (SS) was tested to have a FPF of 9 ± 1% using the full set of Andersen cascade impactor (ACI) and a modified Rotahaler® capable of achieving 4.0 kPa pressure drop at 60 L/min air flow rate. A truncated ACI comprising the USP throat, pre-separator, stage 0, stage 4, stage F, polytetrafluoroethylene funnel (TF) and small collection plate (sCP) was found to be capable of achieving a FPF of 9% collected on TF and sCP. An adhesive tape was used to collect the FPF from the TF and sCP and held in place by an enhancer cell in a 200 mL round bottom vessel containing 50 mL Gamble's solution with 0.2 v/v, % Tween 80. Dissolution testing of SS and Seretide® showed burst release of SS and salmeterol while sustained release of fluticasone. This study demonstrated a reproducible method which may be used for evaluation of the full FPF of orally inhaled products.

1. Introduction

Dissolution testing in the pharmaceutical industry is a well-accepted requirement for oral solid dosage forms, and is routinely required for biopharmaceutical quality assurance of oral products. However, for inhaled solids, although dissolubility of the drug particles is of immense interest, there is still a lack of a universally accepted dissolution methodology for the estimation of dissolution behavior of an orally inhaled product (OIP) to date.

The lung is the natural target drug delivery site for the treatment of various pulmonary diseases such as asthma and chronic obstructive pulmonary disease where local treatment of the disease is desired. As the lung consists of large and extensively vascularized surface area with a thin epithelial barrier, it provides the advantage of rapid absorption of therapeutic agents while bypassing the first pass metabolism as the lung tissues have relatively low enzymatic activity present (Garcia-Contreras and Smyth, 2005). These advantages have also led to the pulmonary delivery of systemic therapeutic agents. Peptide based drugs such as insulin (Ledet et al., 2015), human growth hormone (Walvoord et al., 2009) and heparin (Trapani et al., 2013) have been reported to reach the systemic circulation following aerosol administration. With increased interest for drug delivery via the pulmonary route, the development of a convenient and reflective dissolution method for OIPs would allow for the comparison of drug release profiles between various formulations.

Designing a dissolution system representative of drug particles dissolving in the lungs is challenging due the difficulties in replicating the conditions in the lungs as well as some associated technical difficulties. Dissolution testing of OIPs should ideally be conducted only on the particles which will reach the site of absorption and not the entire formulation. This would require pre-fractionation of the inhaled therapeutic agent into the effective aerodynamic size fraction before dissolution testing. The exact composition of alveolar fluid is also uncertain and the volume estimated is about 10–20 mL/ ~ 100 m^2 of surface, which suggests that the surface is more stagnant compared to the gastric model (Gray et al., 2008; Henning et al., 2010). The presence of endogenous surfactants may also be challenging to replicate (Son et al., 2010).

The clinical efficacies of OIPs have been largely dependent on drug disposition studies with the use of a size-classifying impactor, which will provide an estimate of the actual dose deposited at the targeted site in the lungs. The fine particle fraction (FPF) of the inhaler formulation has generally been accepted to include particles of the aerodynamic size fraction of 1–5 μm which is deposited in the deep lungs. Thus, only a fraction of the emitted dose will reach the intended site for pharmacological action and ideally, a dissolution test designed should only involve the FPF. However, due to the fineness and highly electrostatic nature of the micronized actives making up the FPF (Gray et al., 2008),

* Corresponding author.
E-mail address: phapaulh@nus.edu.sg (P.W.S. Heng).

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most dissolution procedures were conducted on unfractionated powders. These powders were either directly dispersed into an Apparatus 2 dissolution tester (Asada et al., 2004) or placed into modified baskets to prevent drug escape (Jaspart et al., 2007; Learoyd et al., 2008). Micronized actives in pulmonary formulations can also be difficult to be dispersed and may stick to surfaces within the dissolution setup.

According to the Noyes-Whitney equation, particle size is one of the factors affecting dissolution rate. Dissolution of OIPs was also shown to abide by the equation, with the smaller size fraction having a faster dissolution rate (Mees et al., 2011). Thus, for a more accurate estimation through *in vitro* dissolution of inhaled particles, various methods have been developed to collect the FPF for dissolution purposes. Using the Andersen cascade impactor (ACI), Davies and Feddah (Davies and Feddah, 2003) collected a fraction for dissolution on a fiber glass filter insert placed within the ACI while Arora et al. (Arora et al., 2010) collected the fraction on polyvinylidene difluoride membranes that were placed on overturned stainless steel collection plates on stage 4 to collect particles of 2.1–3.3 μm aerodynamic particle size at 28.3 L/min. For the next generation impactor (NGI), membrane inserts have been used for the collection of the aerosolized particles (Son et al., 2010; Son and McConville, 2009) at different stages to collect particles within the FPF size range. Dose collection is a major challenge as most techniques are still unable to collect the full FPF fraction for dissolution testing.

Other than the conventional dissolution apparatus for oral solid dosage forms, the flow-through cell apparatus (Davies and Feddah, 2003; Salama et al., 2008), Transwell® system apparatus (Arora et al., 2010) and the Franz cell apparatus (Salama et al., 2009; Salama et al., 2008) are also being investigated for use for the dissolution of OIP. These methods allow for the use of a small volume of dissolution medium during the testing process. However, methods such as the Transwell® involve the use of a membrane filter that may pose extra hindrance to diffusion, thereby artificially prolonging drug release.

The enhancer cell (Agilent Technologies, USA) is a dissolution accessory that is commonly used for dissolution testing for semisolids. It acts as a holder for the semisolid while providing a fixed exposed surface area for dissolution to occur. The use of the cell as an accessory for dissolution testing of OIPs will be investigated in this study.

The objective of this study is to develop a robust and reliable FPF dose collection system for the purpose of dissolution testing of OIPs with the small volume paddle-over-enhancer-cell dissolution method.

2. Material and methods

2.1. Materials used

Salbutamol sulfate (SS; Fine Drugs and Chemicals Ltd, India), micronized fluticasone propionate (FP; Jayco Chemical Industries, India) and micronized salmeterol xinafoate (SX; Jayco Chemical Industries, India) were used as model inhalation drugs. Commercially available inhalation grade α-lactose monohydrate (Inhalac® 230, Meggle Pharma, Germany) carrier particles were used as provided. High performance liquid chromatography (HPLC) grade acetonitrile, methanol (Tedia, USA) and ultrapure water (Milli-Q, Milipore Corporation, USA) were used as the HPLC mobile phase. Acetic acid (Merck, Germany), sodium dodecyl sulfate (Fluka, Honeywell Research Chemicals, USA) and sodium acetate (Sigma-Aldrich, USA) were used for the buffer.

Magnesium chloride, sodium chloride, potassium chloride, disodium hydrogen phosphate, sodium sulfate, calcium chloride dihydrate, sodium citrate dihydrate (Merck, Germany), sodium hydrogen carbonate (Fluka, Honeywell Research Chemicals, USA), Tween 80, sodium acetate and deionized water (Milli-Q, Milipore Corporation, USA) were used to prepare the dissolution medium.

Seretide® 50/100 Diskus® (GSK, UK) was obtained commercially from a retail pharmacy and used as a model inhaler for the dissolution studies.

2.2. Preparation of dry powder formulation

2.2.1. Micronization of salbutamol

Micronized SS (d_{50} = 5.8 μm) was produced by jet milling (100 AFG, Hosokawa, Germany) with a grinding air pressure of 4 bars and a classifying wheel speed at 20,000 rpm.

2.2.2. Blend preparation

A 2%, w/w SS dry powder blend was created by weighing out the drug and the lactose carrier (d_{50} = 112.2 μm) amounting to 1.5 g in a glass tube and mixed on a vortex mixer (WhirliMixer™, Fisons Scientific, UK) for 10 min. After the blend was created, analysis of drug content uniformity was conducted on ten random samples of 30 mg using ultraviolet spectroscopy (U-5100, Hitachi, Japan) at 274 nm and the coefficient of variation was found to be less than 3%. Samples of 30 ± 1 mg were then filled into capsules (Size 3, Qualicaps, Japan) to form single unit dosages to be used together with a Rotahaler® (Glaxo, UK).

2.2.3. Aerodynamic size determination

Each collection plate of the ACI was first coated with a thin layer of 1%, w/w silicone oil in cyclohexane and allowed to dry before assembly. A modified Rotahaler® and modified Seretide® capable of achieving a pressure drop of 4.0 kPa at a flow rate of 60 L/min was used. Air was drawn through the ACI at 60 L/min for 4 s for each test. The test was repeated for a total of 6 and 10 doses of 2% SS dry powder blend and modified Seretide® respectively. The Rotahaler®-mouthpiece, pre-separator and the collecting plates containing SS was rinsed with water and assayed for drug content using ultraviolet spectroscopy. Collection plate containing FP and SX was rinsed with methanol:water (70:30) and assayed for drug content using HPLC (SIL-10AD VP, LC-20AT VP, Shimadzu, Japan). HPLC methodology will be further discussed in Section 2.4.4. The FPF was then determined from the dose collected from Stage 1 to Stage 4 which represented the aerodynamic particle size fraction between 1.2 μm and 4.4 μm.

2.3. Set up of truncated ACI

After the FPF for the formulation was determined, various interstages were removed in an attempt to truncate the ACI. The use of a truncated ACI allows for the simplified dose collection process as the FPF will be concentrated on a single stage. A polytetrafluoroethylene funnel (TF) with a 17.5 mm wide opening was fabricated and placed at the filter stage (Stage F) with a small collection plate (sCP) under the opening to collect the drug (Fig. 1). The sCP was surrounded by an acrylic ring of 2.2 cm height to help disrupt the airflow and encourage drug deposition on to the silicone oil coated sCP (Fig. 1).

2.3.1. Optimization of truncated ACI conditions

Optimization study was conducted using the SS blend and was focused on 3 main factors: pressure drop across inhaler, air flow rate and the intermediate stage above TF. To vary the pressure drop across inhaler, air flow rate was varied at 40 L/min, 60 L/min and 80 L/min while using the same modified Rotahaler® capable of achieving a pressure drop of 4 kPa at 60 L/min, denoted as $40L_{2.0kPa}$, $60L_{4.0kPa}$ and $80L_{7.5kPa}$ respectively.

For constant pressure drop across different air flow rate, the extent of perforation of the Rotahaler® was modified and tested at 40 L/min, 60 L/min and 80 L/min air flow rate, denoted as $40L_{4.0kPa}$, $60L_{4.0kPa}$ and $80L_{4.0kPa}$ respectively.

As the intermediate stage above TF determines the air velocity within the ACI, stages 2, 4 and 6 were used for to determine the optimal air velocity for FPF deposition on TF and sCP. These were denoted as $60L_{S2}$, $60L_{4.0kPa}$ and $60L_{S6}$ respectively. The inhalation time used for all test was adjusted based on each air flow rate required to achieve 4 L of air to pass through the ACI.