Directly Probing the Dynamic Behaviour of Particles Originating from DPI and MDI Starting Formulations

Allen Haddrell[1], David Lewis[2], Tanya Church[2], Jonathan Reid[1]

[1]University of Bristol, Bristol, UK

[2]Chiesi Farmaceutici S.p.A., Chippenham, UK

Summary

How deep in the respiratory tract a pharmaceutical aerosol penetrates is dependent on the size of the particle at the point of inhalation, its composition, and the microphysical processes that occur during inhalation. The aerosol composition influences the degree to which particles grow when inhaled directly, affecting the deposited dose and pattern. An understanding of the dynamic behaviour of inhalable aerosol is expected to be critical to predicting regional and total dose, which in turn will affect overall efficacy. Meaning, there is the potential to tailor the dynamics of pharmaceutical aerosol, through including trace quantities of additives to the starting formulation, to deliver the desired dose to a specific region in the lung.

Previously, precise measurements of pharmaceutical aerosol's thermodynamics (e.g. hygroscopic growth from dry to >99% relative humidity (RH)) and dynamic (rapid size change resulting from changes in RH) has been demonstrated for nebulizer formulations. To be presented here is the expansion of this technology to directly measure the dynamic behaviour of aerosol originating from metered dose inhaler (MDI), and dry powder inhaler (DPI) starting formulations. These measurements include: (1) the dissolution, in the aerosol phase, of DPI particles and, (2) the rapid evaporation of volatile species from droplets from MDI starting formulation, to saturated water droplet, to final particle. The time scale for these processes was observed to be on the same order as that of a single breath, meaning they will directly impact their deposition pattern in the lung.

Key Message

We have developed the instrumentation to directly probe the dynamic behaviour (e.g. rapid evaporation and dissolution) of pharmaceutical aerosol produced from DPI and MDI starting formulations in relevant environmental conditions (e.g. ambient pressure, temperature and RH).

Introduction

The deposition pattern within the respiratory tract is dependent on the time-dependence of the aerosol size distribution as the aerosol penetrates deeper into the lung. The size of a droplet at the point of generation, the reduction in droplet size resulting from the net loss of propellant/solvent during transfer from the device to the mouth, and any hygroscopic growth on inhalation all could have an effect on total and regional dose. To design active pharmaceutical ingredient (API) formulations for targeted dose, one must have a detailed understanding of these three phases, and the interplay between them. As an example, for metered-dose inhalers (MDI), the rapid evaporation of HFA and ethanol will drastically decrease the temperature of an aerosol droplet. The reduction in temperature will cause it simultaneously to take up water while still losing solvent. Such a complex process in an MDI plume is not well understood, yet vitally important to understanding particle size distributions and the deposited dose. Following the change in MDI propellants from chlorofluorocarbons (CFC) to hydrofluoroalkanes (HFA) dictated by the Montreal Protocol, the average starting droplet diameter was reduced from 2.5-3.8 microns to 1-1.2 microns, improving dose delivery from 10-20% to 52-68%[1].

A consensus forum of industrial, academic and regulatory experts identified a poor understanding of the relationships between physicochemical characteristics of drug formulations and performance in the humid environment of the respiratory tract as one key barrier to progress in inhalation therapeutics[2]. Thus, quantifying the properties of pharmaceutical aerosol that govern dynamic behaviour prior to and during inhalation will yield the potential for the rational design of new formulations for drug delivery to the lung.

The delivery of an API from a starting formulation to the deep lung involves four phases: aerosol generation, transport from the aerosolization device to the mouth, inhalation, and concludes with deposition. The deposition rate in the lung is controlled by the aerodynamic diameter of the droplet at the time of deposition. Thus, the size of the droplet at the point of generation, the reduction in droplet size resulting from the net loss of volatile mass (if present) during transfer from the device to the mouth, and any hygroscopic growth on inhalation will have an effect oin total and regional dose. The development of an instrument capable of directly measuring the interplay between these complex processes will be reported here.

Formatted: Font: Italic, No underline

Formatted: Font: Italic, No underline

Formatted: Placeholder Text, No underline

Formatted: Font: Italic, No underline

Formatted: Font: Italic

Formatted: Bottom: 1.25 cm

Formatted: DDL_BodyText

Formatted: Font: Italic

Experimental

The comparative kinetic electrodynamic balance (CK-EDB, figure 1A) was used in this study to measure the hygroscopic properties/dissolution dynamics of surrogates of ambient aerosol. Our aim in this paper is to present and benchmark the most recently developed capabilities of this instrument. As such, we provide a brief summary of the instrument and its origins, summarise the new capabilities, and then provide benchmarking data of these new capabilities in subsequent sections.

The ability of a direct current (DC) field to suspend droplets has been used since the days of the Millikan oil droplet experiment, with marked improvements in the method being continually made over the century since. Notable developments have included the coupling of an alternating current (AC) field to the DC field to add a restoring force that focuses the droplet to a confined space. Once confined, the droplet size, relative mass and composition can be readily probed. In this work, we have shaped the electrodes into two pairs of concentric cylinders. As a consequence, the strength of the restoring force in the trap that holds the droplet increases. This device, the CK-EDB, can trap and confine a droplet dispensed only <100 milliseconds before. The trapped droplet is illuminated with a laser beam and the angularly scattered light collected by a camera. The angular spacing of elastic light scattering fringes is used to estimate the droplet size. Once trapped the absolute radius of the droplet (when the droplet is spherical) can be measured at a frequency of 100 Hz (Figure 1B). The absolute radius of a rapidly drying droplet can be accurately measured (size accuracy under +/-50 nm).

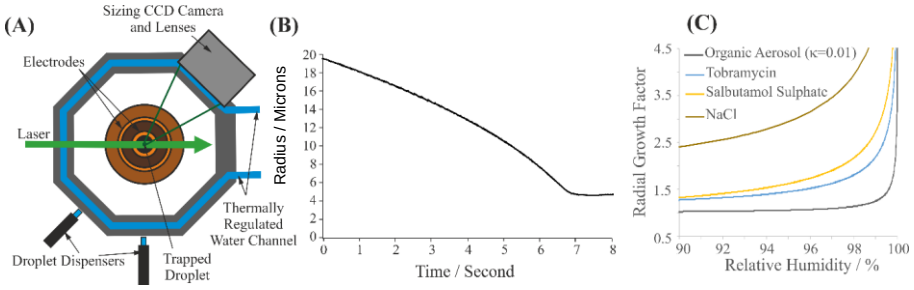

Figure 1. (A) Key components of the CK-EDB. (B) The measured radius of the droplet as a function of time. This data is then used to calculate (C), the hygroscopic properties.

A droplet dispenser is used to generate the droplet and, thus, absolute chemical composition of the droplet is known throughout the entire process, allowing for the direct comparison between the experimental data with a mass flux model[3]. The airflows in the CK-EDB enable the RH and temperature that the droplet experiences to be rapidly changed, making direct observation of aerosol growth kinetics possible, analogous to that experienced in the lung.

The droplet dispenser is functional at temperatures under -100 ºC. This makes the analysis of the rapid mass flux of droplets originating from metered dosed inhalers (MDI) formulations possible. The ability to directly monitor the mass flux from a single droplet made up of the starting MDI formulation is unique to this technology. In these experiments, the focus will be on the kinetics of water/co-solvent loss and gain.

Dry particles are directly injected and trapped in the CK-EDB. A dry needle is first coated with the DPI powder, then positioned near the centre of the CK-EDB. 1 kV pulse is then applied to the needle causing the particles on the needle immediately be ejected from the needle and into the trap.

The capabilities that are unique/advantageous to the CK-EDB include:

1) Use of a water droplet to probe the RH of the airflow that the sample droplet is subsequently studied in with accuracy of ±0.1%, an order of magnitude better than conventional RH probes[4].

2) Direct measurement of the dynamic behaviour of a droplet of known composition in a static and/or variable environment (<100 milliseconds, figure 1B)[4].

3) Accurate determinations of the radial growth factor, a measure of the equilibrium hygroscopic growth of the aerosol as a function of gas phase RH across a range of RH from dry to >100%, and with temperature ranging from <50ºC to <-30ºC (figure 1C). Reaching supersaturation has yet to be published.

4) The conditions, both temperature and/orRH, that the droplet experiences in the trap can be rapidly changed (<0.1 seconds). These features are unique to this technology and are critical in being able to directly mimic the conditions that a pharmaceutical aerosol experiences prior to and during inhalation. Rapid changes in temperature has yet to be published.

5) The dynamics of a single pharmaceutical aerosol droplet/particle originating from DPI and MDI solutions can be measured. This is a newly reported feature of this technology and enables the detailed parameterization of the

physicochemical properties that govern the dynamic properties of these inhalable species, and that key to be able to predict total and regional dose. This has yet to be published.

Results

We now provide new benchmarking data of the performance of the instrument. The ability to simultaneously control and rapidly change both the relative humidity and temperature that the droplet experiences is a unique feature of the newly designed CK-EDB. The impact of isolated changes in RH and temperature on the evaporation rates of pure water droplets are shown in Figure 2. The change in environmental condition is evident from the change in the evaporation rate of a single droplet as the conditions are change.

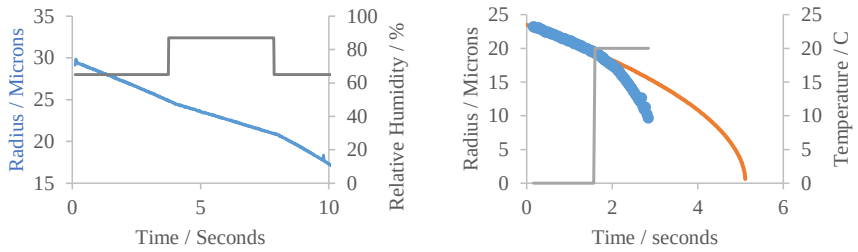

Figure 2. The rapid change of relative humidity (left) and temperature (right) that a single levitated water droplet in a CK-EDB experiences. The orange line on the right indicates a model prediction for an evaporating water droplet into air set at a temperature of 0°C and a relative humidity of 0%.

Such measurements also allow for detailed measurements of particle dissolution as there is a clear, and measurable, point in time that the particle experiences a change in relative humidity. Preliminary data demonstrating the timescale for the dissolution of a single crystalline sodium chloride particle is shown in Figure 3, the very first dynamic measurement of the dissolution kinetics of a crystalline aerosol particle.

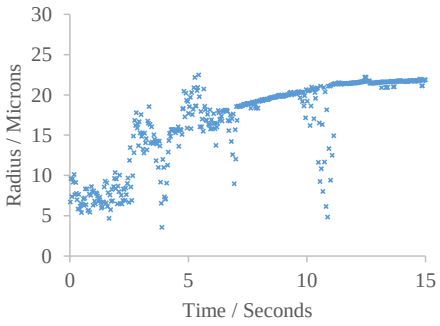

Figure 3. The dissolution of a sodium chloride particle. The relative humidity is increased from dry to >80% at 0 seconds (<0.1 seconds for the RH change to occur). When the particle is non-spherical, it is not accurately sized. It takes 7 seconds for the dry sodium chloride particle to completely dissolve into a spherical droplet.

The ability to accurately determine the size the droplet in the CK-EDB is dependant on the droplet being spherical. As a result, when the particle is dry, much more noise in the data is observed (all data under ~5 seconds). This does, however, give a clear indication of the point where the solid particle becomes a spherical droplet (in this case, ~7 seconds), after which, it's physicochemical properties are much more well understood.

The rapid evaporation of the volatile components within an MDI starting formulation will result in the droplet rapidly cooling to temperatures below 0°C. The resulting change in vapor pressure causes water vapour to rapidly deposit onto the particle. Direct measurements of this complex process are readily made with the CK-EDB (figure 4). Here we present measurements of the evaporation kinetics of a volatile ethanol droplet containing an API in a humid atmosphere.

Formatted: Font: Italic, No underline
Formatted: Font: Italic, No underline
Formatted: Placeholder Text, No underline
Formatted: Font: Italic, No underline
Formatted: Font: Italic

Formatted: Font: Italic

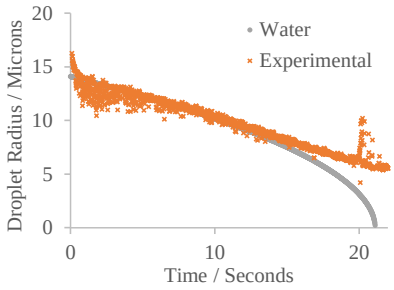

Figure 4. Size of a droplet originally made of Formoterol Fumarate Dihydrate dissolved in ethanol (orange Xs) injected into an airflow with a relative humidity or 81%. The grey line is a model of the size change of a water droplet injected into an airflow with a relative humidity of 81%.

The ethanol present in the starting droplet rapidly evaporates, as indicated by the curve in the first half second (figure 4). This rapid evaporation directly leads to the uptake of water onto the droplet. Note that no water was present in the starting formulation despite the majority of the dynamic behaviour of the aerosol being best described as that of a water droplet. This data suggests that inhaled aerosol from an MDI starting formulation will contain a significant amount of water throughout its lifetime and will likely never be a dry particle in the respiratory system.

Discussion and Summary

The ability to probe the particles and droplets originating from MDI and DPI starting formulations has been developed. Early notable observations found using this novel technology include:

- Dissolution of sodium chloride particles is a slow process (relative to the time scale of inhalation); this may dramatically affect the overall deposition pattern of DPI particles in the lung.
- Droplets containing highly volatile solvents (including ethanol) such as originate from an MDI are likely to never be dry and will rapidly transition into water droplets during their evaporation into a humid environment (such as the respiratory system). This will have a consequential effect on where the dose is delivered in the lung.

References

1. Leach, C.L.: *The CFC to HFA Transition and Its Impact on Pulmonary Drug Development*. Respiratory Care, 2005: pp1201-1208.
2. Forbes, B. et al.: *Challenges in inhaled product development and opportunities for open innovation*. Adv. Drug Del. Rev. 2010; 63: pp69-87.
3. G. Rovelli, R.E.H. Miles, J.P. Reid and S.L. Clegg: *Accurate Measurements of Aerosol Hygroscopic Growth Over a Wide Range in Relative Humidity*. J. Phys. Chem. A 2016; 120: pp4376−4388.
4. J.F. Davies, A.E. Haddrell, A.M.J. Rickards and J.P. Reid: *Simultaneous Analysis of the Equilibrium Hygroscopicity and Water Transport Kinetics of Liquid Aerosol.* Anal. Chem.; 2013; 85 (12): pp5819-5826.