# Method for Exploring the Evaporation of pMDI Propellant Droplets with Microsecond Time Resolution

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## Key Message

**Ultrafast, single-droplet measurements of pMDI can resolve between evaporation rates of different propellants and water condensing onto evaporating droplets extends liquid aerosol lifetimes to >1 s.**

## Introduction

The transition to **low global warming potential (GWP)** propellants for **pressurised metered dose inhalers (pMDIs)** presents reformulation challenges and opportunities due to differences in their physicochemical properties.[1,2] To control the performance of low GWP propellant-based formulations and demonstrate the equivalence of reformulated products, a deeper understanding of their evaporation kinetics is beneficial as:

- Droplet evaporation directly influences the efficiency of drug delivery as it governs the evolution of aerosol properties during inhalation.
- Aerodynamic size, phase, and composition evolve during inhalation due to coupled heat and mass transfer.
- Lung deposition is a function of aerodynamic diameter, and thus particle shape and density.

Single-droplet studies provide a route to precise measurements of evaporation rates to then expedite reformulation and equivalence studies for pMDIs with novel propellants.

## Objectives

- Develop a measurement technique for volatile propellants that can resolve between individual compounds including HFA 134a, HFA 152a, HFO 1234ze.
- Measure the impact of ambient humidity upon droplet size evolution.
- Compare pMDI propellant evaporation dynamics.

## Methods

To observe evaporation processes which range orders of magnitude in time (from milliseconds to seconds), a dual-measurement approach was used. A modified **stroboscopic droplet analysis (SDA)** technique (**Figure 1**) was utilised for single-droplet-scale measurements of propellant evaporation with sub-microsecond time resolution.[3] SDA was coupled with the previously presented **electrodynamic balance (EDB)** method. (**Figure 2**) to analyse droplet behaviour in elevated humidities over extended timescales. In both cases, the propellants were chilled at ambient pressure to negate evaporation prior to droplet generation. Measurements of pure propellants, HFA 134a, HFA 152a, and HFA 1234ze, without excipients or active ingredients were made. Key attributes of each technique are listed below:

**EDB:**

- High quality aerosol kinetics data
- Tightly controlled experimental conditions, temperature & **relative humidity (RH)**
- Cannot measure early droplet evaporation (<0.1 s)

**SDA:**

- Sub-microsecond time resolution
- Measures size from moment of droplet formation
- Direct imaging of droplets
- Little control of experimental conditions (ambient)

## Results

**Figure 3** presents the initial evaporation of HFA 134a, HFA 152a, and HFO 1234ze droplets measured using the SDA technique. Droplet oscillations may be seen in the initial 0.5 ms of droplet lifetime, arising from the separation of droplets from the bulk. An elevated evaporation rate is noted over this period compared to the rest of the data, particularly for HFA 134a. The HFO 1234ze measurements are less self-consistent than other samples, likely due to variation in ambient conditions as droplets are exposed to the laboratory environment. Measurements show droplets of different initial size, but as evaporation rate is a size-independent parameter, it is comparable across datasets. Evaporation rate is calculated from the 'R-squared' law definition as the negative of the gradient of a linear fit to radius squared versus time. The results of these calculations are also shown in **Figure 3**.

EDB measurements of HFA 134a and HFA 152a droplet evaporation are presented in **Figure 4**. In all cases, dry particle formation was not observed. Instead, initial water condensation onto evaporating propellant droplets was indicated by aqueous droplet formation. Subsequent water evaporation was then observed, with steady-state, RH dependent evaporation. The evaporation of propellants was not captured by these measurements as it occurred prior to trapping. The data in **Figure 4**, demonstrate that at both 50 % and 90 % RH, condensed water extended the persistence of propellant-initiated droplets, which maintained larger sizes for a matter of ~ 1 s as opposed to completely evaporating within ~ 1-10 ms.[5] Trapping of HFO 1234ze droplets remains unachieved due to a lower dipole moment; further work will extend the EDB capabilities to more propellants.[2]

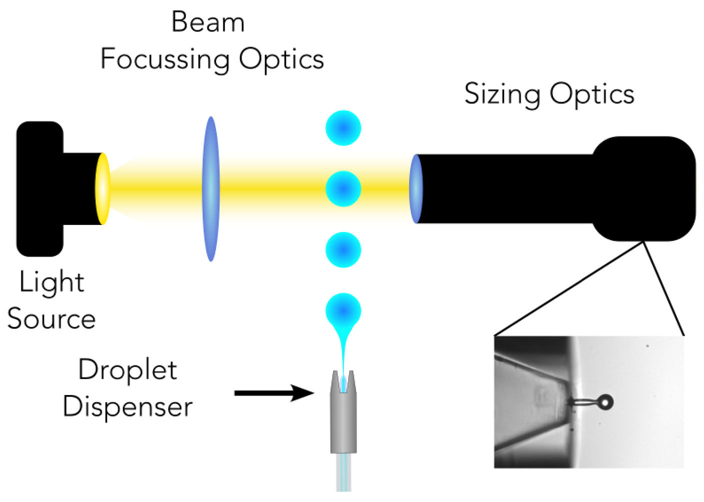
| Propellant | RH / % | $R_{0,\,Water}$ / µm | $\Delta H_{Vap}$ | $R_0$, HFA / µm |
|---|---|---|---|---|
| HFA 134a | 50 | 10.94 | 47.52 cal/g | 23.0 |
| | 90 | 9.95 | | 20.9 |
| HFA 152a | 50 | 13.10 | 19.08 kJ/mol | 26.5 |
| | 90 | 13.47 | | 27.3 |

▲ **Table 1**: Initial radii, $R_0$, of aqueous droplets measured with the EDB, and the calculated corresponding initial radii of precursory propellant droplets.

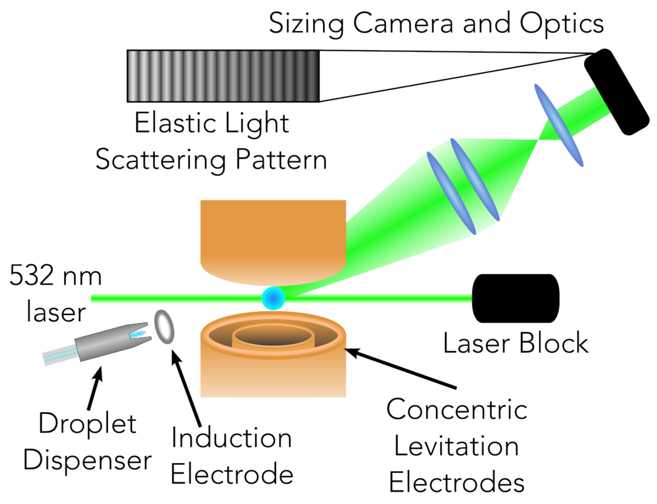
The initial propellant droplet size was determined from the initial calculated size of the water droplets (**Figure 4**), using an evaporation-condensation energy balance (values in **Table 1**). Combining these initial sizes with the SDA-measured evaporation rates enabled a lower limit for droplet size to be evaluated, shown in **Figure 5**.

## Conclusions

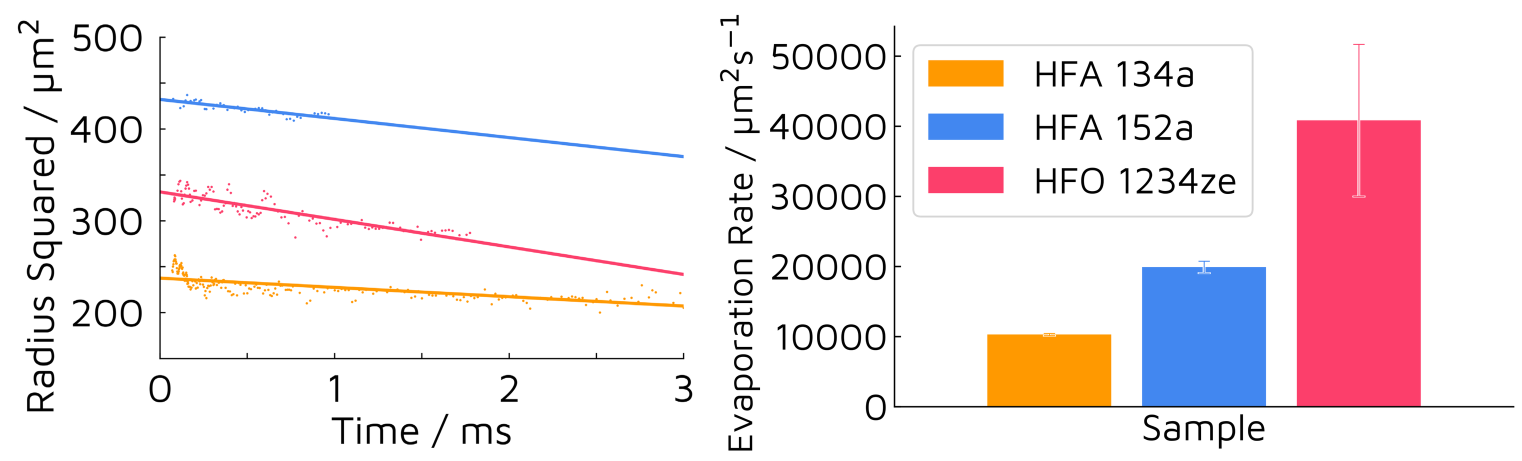
- Direct measurement of propellant droplet evaporation is possible at the single droplet scale - **this provides a route to evaluate differences in in-vitro performance between different propellant formulations**
- Evaporation of HFO 1234ze is ~4 times faster than HFA 134a and ~2 times faster than HFA 152a
- Water condensation results in non-negligible changes to evaporation dynamics, even in sub-saturated RH.



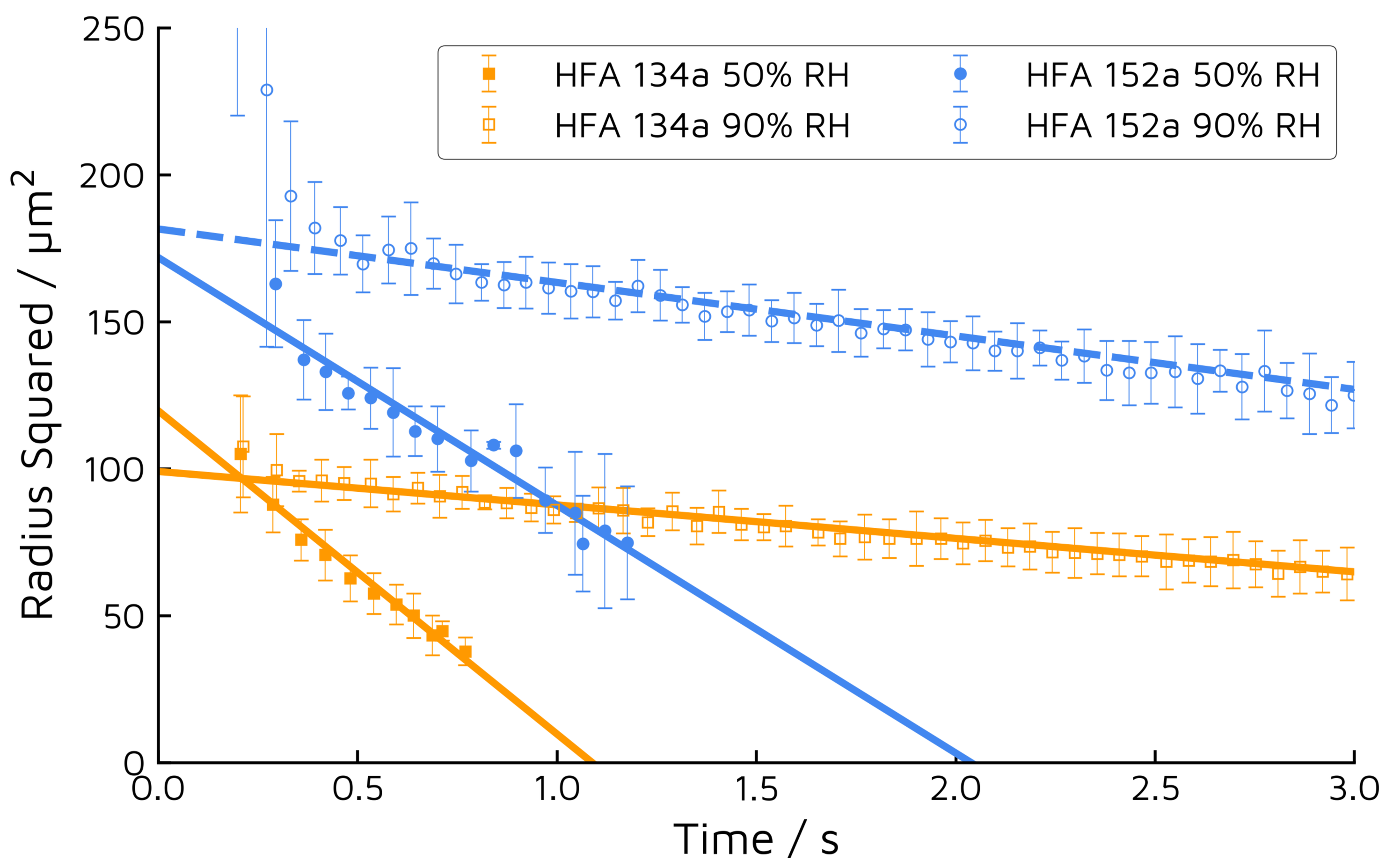

▲ **Figure 1**: A top-down diagram of the SDA experimental setup. A stream of uniform droplets is generated by a droplet-on-demand dispenser and imaged using stroboscopic imaging. An example image sequence covering the initial ~200 µs of droplet formation is shown.



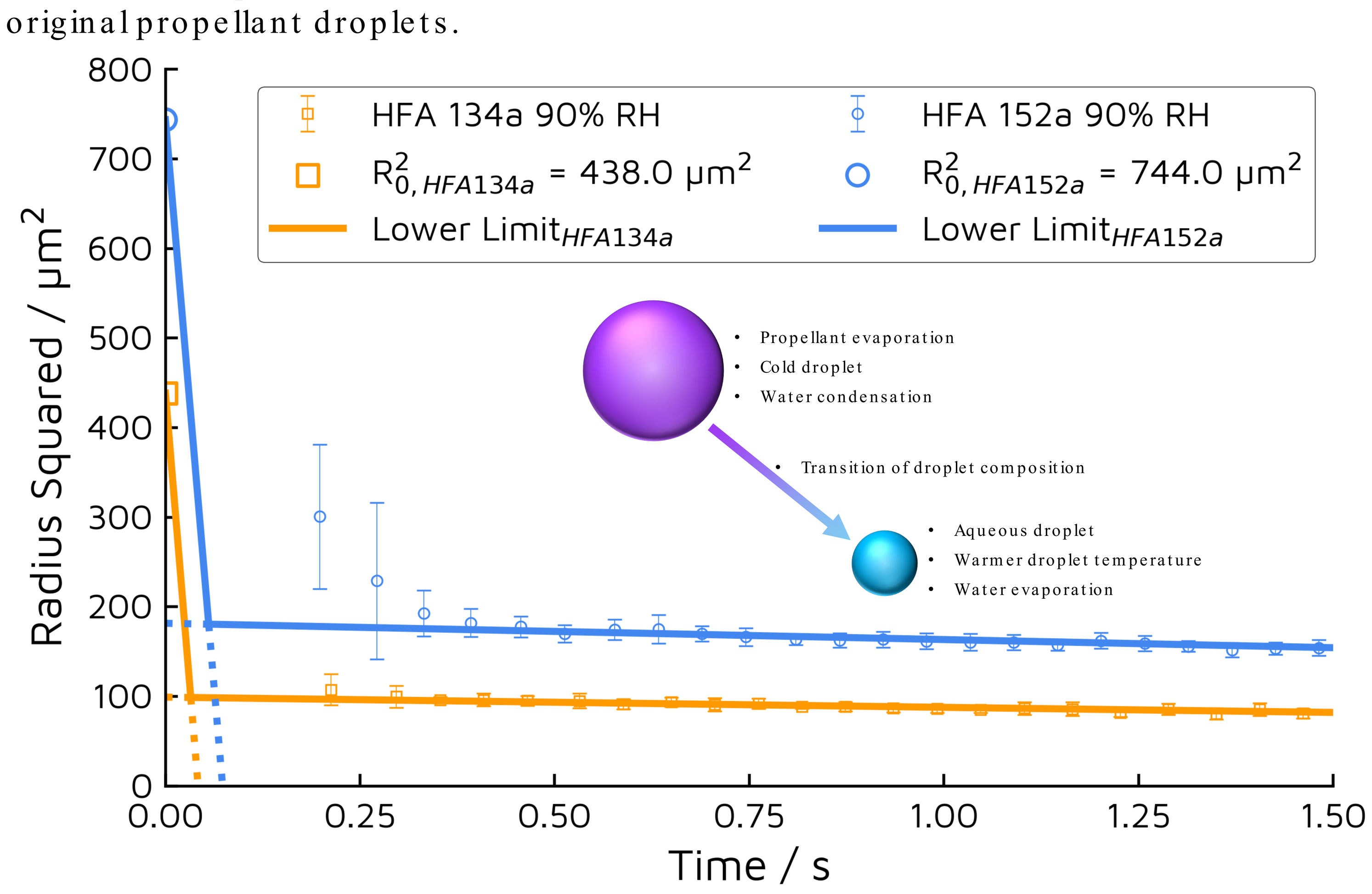

▲ **Figure 2**: A simplified diagram of the EDB setup. Droplets are generated, charged, and trapped in an electrodynamic field. Laser light scattering is collected and analysed to calculate droplet size.




▲ **Figure 3**: Left: SDA measurements of propellant evaporation with linear fits applied to smooth oscillatory droplet behaviour and experimental noise. Right: Evaporation rates of propellants calculated from the gradient of the linear fits. Mean and standard deviation of two measurements shown for each sample.




▲ **Figure 4**: EDB measurements of droplet size change over time for droplets initially composed purely of propellants. Points and error bars are mean and standard deviation for three repeats per sample. Linear fits are applied and back-extrapolated to evaluate the initial radius of water droplets corresponding to the observed evaporation. These values are then used to calculate the size of the original propellant droplets.




▲ **Figure 5**: Propellant evaporation profiles in 90 % RH, calculated using $R_0$ from Table 1, propellant evaporation data from SDA (**Figure 3**) and EDB (**Figure 4**, points and error bars are mean and standard deviation for three repeats per sample.). A lower limit for droplet size is defined by evaporation rates of the propellant and remaining aqueous droplet, with a transition at the intersection. Also shown is a diagram of the key features of droplet composition evolution.

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