Understanding What Happens to Aerosols on Inhalation: Dynamics of Size and Compositional Change

Jonathan P. Reid[1], Allen E. Haddrell[1], David Lewis[2] & Tanya Church[2]

[1]School of Chemistry, University of Bristol, Bristol, BS81TS, United Kingdom
[2]Chiesi Limited, Bath Road Industrial Estate, Chippenham, Wilts, United Kingdom

Summary

In inhalation therapies, many microphysical processes can occur on timescales directly comparable to timescales for inhalation and exhalation. The uptake and loss of water, propellant evaporation, co-solvent evaporation, dissolution of crystalline or amorphous particles, and particle coalescence may all occur for newly formed particles emitted from drug delivery devices such as dry powder inhalers (DPIs), metered dose inhalers (MDIs) and nebuliser systems. Although analysis of residual particles can be routinely achieved, many of the processes occurring in the aerosol phase are not amenable to investigation by conventional techniques, requiring the development of new approaches to more fully establish the factors that control aerosol particle deposition, disposition and, ultimately, efficacy. Here, we present microphysical aerosol particle measurements that directly allow access to the timescales, environmental conditions and particle sizes that must be addressed when understanding what happens to aerosol particles from the point of generation to deposition. In particular, we explore the dynamics of water transport, specifically the kinetics of water transport to and from particles during condensational growth or evaporation. To quantify the size-dependent changes that can be expected on inhalation, it is necessary to both determine the capacity of particles to grow by absorbing water as a function of the environmental relative humidity and temperature, and the timescale for particle size change. Thus, we report measurements of the equilibrium growth (the capacity) of a range of typical excipients and pharmaceutical ingredients (e.g. drug, lactose, and other excipients) and the kinetics of water condensation. In addition, we suggest mechanisms by which the timescale of growth can be actively controlled and tuned to be slower than the inhalation/exhalation time.

Introduction

Aerosol particles are dynamic, continuously changing in size, phase and composition with time in response to changes in local environmental conditions such as relative humidity (RH) and temperature. Dependent on particle size (and, thus, surface-to-volume ratio), composition, and phase, these changes can span timescales from millisecond to minutes or longer.[1–3] In inhalation therapies, a number of processes in the aerosol phase compete. Propellants and co-solvents evaporate from newly formed droplets from, for example, pressurise metered dose inhalers (pMDI), due to their absence in the surrounding gas phase.[4] Water from aqueous aerosol generated by nebulisers may first evaporate, due to the mismatch between the water activity in the condensed phase and the sub-saturated environmental RH (<100 %), before re-condensation occurs as the aerosol passes into the respiratory tract experiencing extremely high RHs and even supersaturated conditions.[5] Solid crystalline or amorphous particles may dissolve by absorbing moisture from the gas phase leading to dissolution[6] even before deposition. Particles delivered from inhalation devices may interact, both competing for the available gas phase moisture and coalescing to form larger particles and reducing the particle concentration. These processes can all occur on timescales much shorter or comparable to the inhalation/exhalation time. Indeed, particle size, composition and phase may be continually evolving and never establish a steady state.[1]

The analysis of aerosol particles used in inhalation therapies is challenging due to the extremely small sample volumes (a 1 μm particle has a volume of just 0.5 fL, 0.5×10^{-15} L, and a mass of 0.5 pg, 0.5×10^{-12} g), the short timescales over which changes in size, composition and phase occur, and the challenges of developing non-invasive techniques that do not perturb the state of the particle. Most measurements are instead made on ensembles of particles (large collections) using impactors, optical counters and mobility sizers.[7] Necessarily, particles collected are residual particles, what remains once all of the volatile and semi-volatile components have been removed. Control over RH and temperature is often attempted but reproducible measurements can only be achieved if reproducible aerosol loadings and environmental conditions are established. Slight changes in particle number concentrations can be expected to significantly influence the competition for available moisture across a particle size distribution, thereby impacting the breadth of the size distribution and the degree to which all particles are able to grow. Indeed, slight changes in RH and temperature can change the availability of moisture and it is challenging to achieve environmental conditions that match the temperature and high humidities found in the lung. Finally, the analysis of particles at varying times after sampling can lead to artefacts and ambiguities in understanding particle phase, size and composition.

Such end-of-line measurements allow comparison of the performance of varying formulations and devices in delivering desired residual particle size fractionations, and correlations with dose and potential efficacy can be established. However, although these relative measures can be invaluable, important questions remain that could allow a more comprehensive understanding of the drug delivery process and routes to improve efficacy.[8] How can these single-point measurements be related to the inherent complexity in aerosol particle size, composition and phase that can be expected to occur between the points of aerosol generation and deposition? How does the generation mechanism of the aerosol (e.g. pMDI, dry powder inhaler or nebuliser) and formulation impact on the state of the aerosol at the point of inhalation, and what influence does this have on the aerosol-lung interaction? What is the disposition (dissolution, absorption, metabolism, etc) of the aerosol at deposition and how does this then impact on pulmonary pharmacokinetics? If the aerosol processes are well enough understood, to what extent can we exploit the properties of aerosols to refine drug delivery and improve delivered dose? In this paper, we consider just process occurring during inhalation, the hygroscopic growth of inhaled aerosol particles.

The Hygroscopic Growth of Aerosol

The dynamic processes of water condensation on inhaled particles that leads to hygroscopic growth has long been considered to play a role in determining total and regional deposited dose.[9–11] Löndahl and coworkers have explored extensively the impact of particle hygroscopicity (the capacity of an aerosol particle to absorb water) on deposited fraction for particles smaller than 500 nm diameter.[12–14] For example, they concluded that a person during exercise exposed to hydrophobic particles (low capacity to absorb water) of 100 nm diameter can be expected to receive a dose sixteen times the dose of a person at rest exposed to hygroscopic salt particles.[12] Deposited fractions of hygroscopic particles could be rationalised if the RH in the lung was assumed to be 99.5 % and particle growth by water condensation was assumed. For particles in the size range 1 – 5 μm which were unresponsive to water vapour, they determined an increase in the deposited fraction from ~0.4 to 1.0.[14] Indeed, Longest, Hindle and co-workers have suggested that the hygroscopic growth kinetics of sub-micrometre could be used to enhance dose and permit the targeting of aerosol deposition.[15–17] In vitro methods have been used to explore the influence of ambient RH on the regional delivered dose from both suspension and solution pMDIs.[18] Accounting for hygroscopic growth on inhalation in models is considered to be essential to model deposition fractions.[11,5,19]

Schematically, we illustrate in Figure 1 the hygroscopic growth process that must be understood on inhalation. On inhalation, the RH rises to close to the saturation RH (>99 %).[20] Indeed, there are some indications that locally the gas phase may become supersaturated with respect to water vapour.[5] In addition, the temperature increases above the ambient surroundings to 37ºC. Typical periods for inhalation are a few seconds. To maintain equilibrium with the gas phase, water condenses onto the aerosol particle population. The *capacity* of the condensed phase to absorb moisture is dependent on the hygroscopicity of the excipients, active pharmaceutical ingredients and additives; more hygroscopic and water soluble components absorb more water, less soluble components generally absorb less water. Clearly, the addition of selected components can facilitate control over the capacity for hygroscopic growth.[21] Concomitant with the increase in water content, the size of the particle increases appropriately. The timescale for condensation can vary from <0.1 s for particles initially less than 1 μm in diameter to much longer than 10 s as the particle size exceeds 5 μm.[22] This timescale can depend on the initial phase of the particle and the presence of surface active species, potentially allowing the control of the timescale for growth.[2,3]

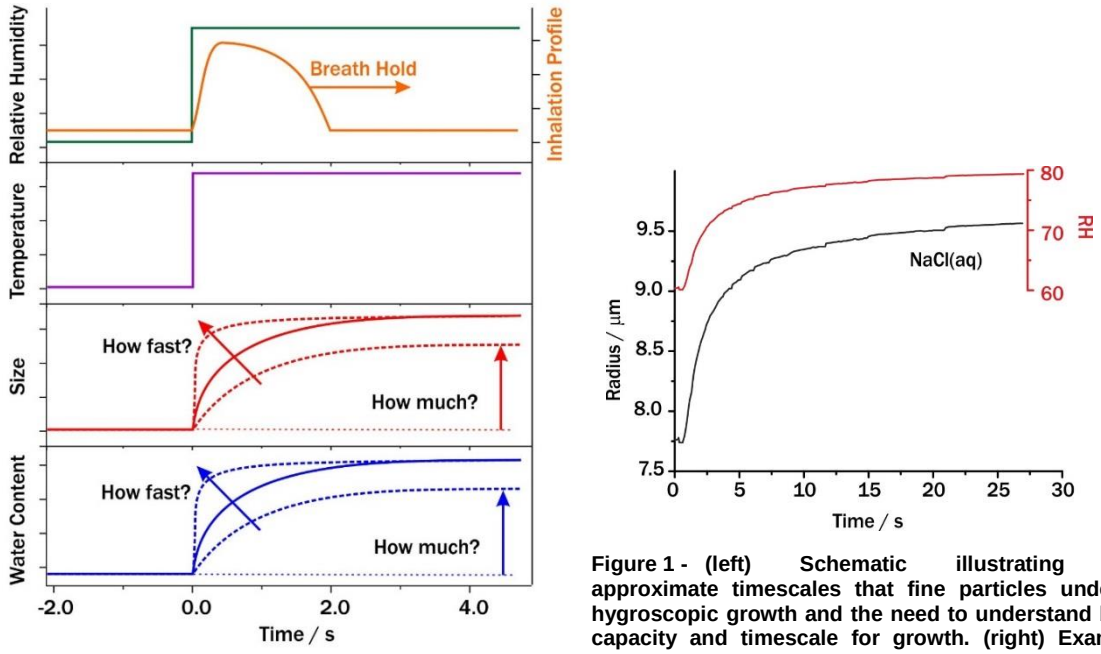

Figure 1 - (left) Schematic illustrating the approximate timescales that fine particles undergo hygroscopic growth and the need to understand both capacity and timescale for growth. (right) Example measurement showing the condensational growth kinetics of an aqueous NaCl droplet.

One method for reporting the capacity of an aerosol component for hygroscopic growth is to report the value of the parameter κ used in κ-Köhler theory.[23] The larger the value of κ, the more hygroscopic the aerosol and the greater growth observed. Saline solution represents one of the most hygroscopic of all aerosol components. Sodium chloride has a κ value of 1.3 and particles can grow by as much as a factor of five relative to their size at an ambient RH of 50 %, depending on the final RH. By contrast, a low hygroscopicity component, $\kappa < 0.01$, may grow by a factor of less than 3 by a RH of 99.7 %.[24] Components that are even considered insoluble may show dissolution and growth at high humidities >99 %,[25] suggesting the absorption of water on aerosol particles and dissolution will occur. Indeed, the condensational growth of water on amorphous solid particles typical of the sizes used in inhalation occurs readily although can be delayed: starting from a viscosity $>10^{12}$ Pa s, condensation proceeds by plasticisation of a viscous core, rapidly decreasing the particle viscosity to <1 Pa s and leading to full dissolution.[26]

Measurements of Aerosol Dynamics and Physicochemical Properties

Simulating in the laboratory the inhalation process aerosols experience during inhalation and measuring dynamic change in aerosol particle size is challenging, requiring sub-second time-resolution, better than ±100 nm size resolution and access to the rapidly changing environmental conditions that occur from generation to deposition. We have developed a method that allows an aerosol particle to be exposed directly to the dynamic changes anticipated on inhalation with accompanying measurements of size, composition and phase.[2,3,27] A particle with a low amount of charge is trapped from a droplet-on-demand generator (or alternative generation mechanism) between two pairs of concentric cylindrical electrodes. A gas flow enters through one pair of electrodes and can be rapidly switched, instigating a change in RH (and potentially T) on a timescale of <0.1 s. The dynamics of particle size change can then be followed; an example is shown in Figure 1 that illustrates the condensational growth kinetics of an aqueous sodium chloride droplet. Not only does this method allow the timescale for aerosol inhalation processes to be directly simulated and probed in the laboratory, providing insight into the exact microphysics that occur, but parallel measurements can provide highly accurate measurements of the hygroscopic growth curves of typical excipients and drug compounds to very high RH close to saturation.[22] Further insight into the mechanism of aerosol transformation during inhalation and how it can be tuned for particular properties and processes can be gained from new methods for accurately and directly determining aerosol droplet surface composition (surface tension) and viscosity.[28]

Summary

Aerosols are dynamic, with particle size, composition and phase expected to respond to the changes in the RH and temperature that occur on inhalation. Advanced experimental techniques now allow us to gain direct insight into these microphysical processes that occur at the single particle level during inhalation. An improved understanding could lead to opportunities to better control and tailor aerosol hygroscopic properties on inhalation.

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