Deposition of Aerosols for Dissolution Experiments: How to Combine the One with the Other?

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Summary
Several in vitro methods have been proposed to simulate the dissolution of inhaled powder drugs in the lungs. These methods prescribe that the aerosol to be tested is collected on a solid surface and then contacted with a liquid dissolution medium. One important question is how to coat the test surface with aerosol in order to prepare for a dissolution experiment that will be as relevant as possible to the in vivo process. Three important aspects of the aerosol coating process are i) the density of deposition of aerosol on the test surface, ii) the deposition pattern aerosol on the test surface, and iii) the relation between the particle size distribution of the tested airborne aerosol and the particle size distribution of the aerosol deposited on the test surface. For two different formulations of the same low-soluble substance it remains unknown to what extent the same dynamic solubility measured in vitro will be accompanied by the same PK pattern following in vivo inhalation exposures.

Introduction
Constituting a complicated mode of administration, inhalation of aerosolized pharmaceuticals is a difficult process to design and control. This is evident both in efforts to achieve a controlled duration of an active substance in the lungs or to achieve bioequivalence between a generic drug and its originator. Even if the same particle size distribution is achieved between two different formulations of the same drug this is no guarantee they will exhibit the same pharmacokinetic (PK) pattern following inhalation exposures (Horhota 2014). Because many long-acting inhaled drugs have low solubility as one parameter controlling their PK following inhalation, there is a great need to develop in vitro methods for simulating the dissolution step of various drug formulations in the lung. One important goal of such a method is that it reasonably mirrors the dissolution/absorption process of single deposited particles in the lungs. There is also a great need to cross-validate these methods against the dissolution/absorption process occurring in vivo.

Major events from inhalation maneuver to systemic PK
The dissolution process is an important step in the overall process when a particulate substance of lower solubility is inhaled into the lungs and absorbed into the circulation. Figure 1 shows an attempt to structure the process when an inhaled drug aerosol enters the lungs up until the corresponding solutes appear in the systemic circulation.
The process can be described as a parallel-serial process where the inhaled aerosol bolus slides along the major airway segments from the trachea to the alveolar region. Particles deposited in each airway segment begin to dissolve and diffuse into the capillary bed below before appearing in the systemic circulation as a mixed output. Major parameters affecting the overall transport in each segment are; i) the diameter of the dissolving particle, ii) its inherent dynamic solubility, and, iii) the thickness and transport capacity of the airway barrier onto which it has deposited. All three parameters are interconnected coupled and should ideally be controlled for separately, but it is the influence of the formulation-specific parameters particle diameter and dynamic solubility that is of particular interest to measure and control.

The complexity of the disposition process is merely indicated in Figure 1, where an innumerable number of parallel transport processes occur between particles deposited at the airway air interface and the circulating blood in the respiratory capillary beds. Profound gradients occur both in average particle size and in air/blood barrier thicknesses with penetration depth into the airways. Yet it seems likely that for low-solubility drugs the specific dissolution rate of similar sized particles will be of importance for the overall disposition process. It is perhaps reasonable to assume that if the dissolution rate of similar sized particles of two low-solubility formulations in the lungs differ significantly they will likely not exhibit the same PK in the systemic circulation. Equally important is the extent to which an identical dynamic solubility measured in vitro will be accompanied by identical PK patterns demonstrated in vivo.

Figure 1: A schematic of the inhalation, deposition, dissolution, and absorption of a soluble particle aerosol in the lungs.
Simulating pulmonary dissolution in vitro

For simulation of the dissolution of inhaled dry powder aerosols in the lungs a number of methods have been published (Riley, Christopher et al. 2012; Börjel, Sadler et al. 2014). In most of them the investigated aerosol is deposited on a test surface or membrane, which is then brought in contact with a liquid dissolution medium into which the solute dissolves. The rate of appearance in the receiving liquid medium is a measure of the simulated dissolution rate in the lungs.

When depositing a study aerosol on the test surface there are two parameters in particular that need attention:

I) Density of deposition of the particles on the test surface
II) Particle size distribution on the test surface compared to that of the delivery aerosol

In a typical inhalation maneuver when 100 µg of a respirable-sized dry powder drug survives throat impaction and enters the lungs, this may correspond to some 25 million 2 µm unit density particles. If 10 million of these are deposited over the whole lung surface area and 5 million deposited in the alveoli, the latter are each most likely to reside alone in an alveolar sac. If the remaining 5 million particles are deposited already in the bronchial tree the average distance between those particles will still be in the hundreds of µm. As a consequence, the dissolution process in vitro should be simulated with particles having dissolution plumes that preferably should not interfere with each other. This is supported by the observation that a similar sized aerosol of the low solubility steroid fluticasone furoate had quite similar dose-normalized absorption kinetics in the isolated perfused lung of the rat when dosed at the two really high levels of 5.6 and 46 µg/lung (Selg, Ewing et al. 2013). Therefore, in the in vitro set ups the density of deposition of particles should probably not exceed the range of single µg/cm² of test surface.

Deposition of particles for dissolution measurements

Many dry powder drugs intended for inhalation administration have delivery aerosols with rather polydisperse particle size distributions. Because particle size has a decisive influence on rate of dissolution of single particles, with smaller particles dissolving faster that larger (Higuchi and Hiestand 1963), dissolution data can be either derived from representative distributions of the polydisperse aerosol, or, from selected size classes of the studied aerosols. With a polydisperse aerosol the question arises whether the size distribution on the test surface should mirror the distribution of the inhaled- or the deposited aerosol? It is the deposited aerosol that collectively will make up the systemic PK pattern. So the method of deposition of polydisperse test aerosols onto the test surface will become important.
To represent the inhaled aerosol a 100% deposition efficiency is necessary from either filtering down the aerosol onto a high-efficiency filter (Davies and Feddah 2003) or by allowing total sedimentation of the test aerosol from a stagnant aerosol (Hein, Bur et al. 2011). To represent the lung-deposited aerosol the test surface needs to present a deposition pattern similar to those of typical airway segments in the lungs. The respiratory tract acts as a low efficiency particle trap with broad and overlapping deposition cut off curves as a function of particle size. These deposition curves will change gradually according to depth into the respiratory tract. So for polydisperse aerosols the aerosol size distribution deposited on the test surface can at best serve as a representative distribution of an aerosol deposited at some level in the lungs. For more polydisperse aerosols it may be preferable to use size-separated aerosols instead. However this will pose further technical challenges. Size separation can either be accomplished directly in line, immediately preceding aerosol deposition on the test surface (Son and McConville 2009), or, size separation may be performed in a separate step before the coating of the test surface. With the first strategy, employment of an impactor providing a high efficiency cutoff for size-classifying the particles, this will require high speed jets that may result in localized deposition patterns of the separated particles. This phenomenon may conflict with the requirement that dissolution plumes from individual particles should preferably not interfere with each other. In the case of size separation in cascade impactors or cyclone batteries preceding the step of aerosolization for coating of the test surfaces, the challenge will be to re-aerosolize the separate particle size classes into disperse aerosols recreating its aerodynamic size. However, if the latter procedure works, it may be possible to distinguish the likely role of the dynamic dissolution rate from the other parameters influencing the systemic PK of inhaled soluble dry powder aerosols. It may also be possible to separate out the effects of composition, such as crystallinic/amorphous structure, from the other major parameters controlling the dissolution rate. Once a method has been established to simulate even the size-specific dissolution rate of particles in the lungs, the question arises of whether two size-equivalent aerosols of a lower-solubility substance having the same dissolution rate will always have the same systemic PK, thus being bioequivalent? In viewing the schematic in Figure 1 it is evident that any mechanism that slightly shifts both the deposition fraction and the depth distribution of aerosol deposition in the lungs will most likely shift systemic PK and therefore fail bioequivalence. One obvious parameter driving such a deposition shift is static electricity of the generated aerosols. Fortunately much progress have been made in investigating the effect of static electricity on deposition of aerosols in the lungs (Kwok and Chan 2009).
References


