The lung as a dissolution vessel?

Do we understand the biorelevance of drug dissolution in the lung?

Jayne E. Hastedt
JDP Pharma Consulting, LLC

Dissolution testing

The United States Pharmacopeia (USP) Dissolution Apparatus 1 (rotating basket) was first introduced in 1970 for oral drug products.[1] The dissolution test is a quality control tool to assess batch-to-batch variation, an aid to formulation development, and a means to link *in vitro* product release profiles to *in vivo* product performance for oral products. The current issues associated with dissolution testing for oral products are: the discriminating power of the method; utilizing test conditions and media that are indicative of the *in vivo* environment; and establishing a link between *in vitro* data and *in vivo* product performance (an IVIVC). Dissolution test apparatuses have evolved over the years and application has expanded to oral controlled release, transdermal, suppository and other novel or nonconventional dosage forms. The Quality by Design (QbD) "desired state" for dissolution testing is to be able to predict the product bioperformance based on *in vitro* data.

Over the past 10+ years, there has been an increased interest in developing dissolution test methods for novel dosage forms. In 2003, the International Federation of Pharmaceutical Sciences (FIP) and the American Association of Pharmaceutical Sciences (AAPS) published a position paper containing guidelines for dissolution testing of novel/special dosage forms.[2] The authors proposed "first choice" test methods using *existing* apparatus for these novel/special dosage forms. A follow-on workshop sponsored by the FIP Special Interest Group (SIG) on Dissolution/Drug Release in conjunction with the Royal Pharmaceutical Society of Great Britain (RPSGB) was held in 2008 on the *in vitro* drug release from special dosage forms. This workshop was the first to specifically discuss the role of dissolution for intranasal and inhalation products.[3] In 2009, another joint workshop sponsored by the AAPS and FIP SIG on Dissolution/Drug Release was held to review the latest advances in dissolution testing for novel dosage forms and resulted in an update to the 2003 publication on this topic.[4] In this publication, the authors noted that although there is not a dissolution test method in place for aerosol products, there might be value in understanding drug release from inhaled particles and droplets deposited in the lung. Over the same period of time, there has been increased interest in developing dissolution test apparatus and methods specifically for inhalation products.[5-7]

Much of the interest in dissolution testing for inhalation products came directly from various

pharma groups as well as regulators. Why the interest in the dissolution of inhalation products? The response to this question results in another series of questions:

- Is particle dissolution a biorelevant critical quality attribute for inhalation products?
- Are the *in vitro* product performance test methods for aerosol particle size distribution and delivered dose uniformity (USP <601>) insufficient to characterize the bioperformance of inhaled, topically-active drugs?
- Can product dissolution test results be used to compare inhalation drug delivery formulations and devices?
- Will dissolution test data provide us with a better understanding of pulmonary drug bioavailability and eventually lead to a correlation between *in vitro* dissolution data and *in vivo* performance for pulmonary products?
- Can dissolution test method experience generated from drugs delivered via oral administration be used for pulmonary drugs?

Regardless of the purpose, before we push further down the path of developing test methods and dissolution apparatuses for pulmonary drugs, let's review the basic principles of particle dissolution and our current knowledge of particle dissolution in the lung.

Particle dissolution

In order for absorption or receptor binding to occur, regardless of the route of administration, a drug needs to dissolve. We know from the Noyes-Whitney equation (Eq. 1) that the dissolution rate of a solid drug is dependent upon diffusivity and solubility in the media of interest, the surface area of the solid wetted by the media and the hydrodynamics of mixing.

$$\frac{dM}{dt} = \frac{DS}{h}(C_s - C) \qquad \text{(Eq. 1)}$$

$$\frac{dC}{dt} = \frac{DS}{Vh}(C_s - C)$$

where D is the diffusion coefficient, M is the mass of the dissolved drug, C is the concentration of the dissolved drug, S is the surface area available for dissolution, C_s is the solubility of the drug, t is time, V is the volume of the dissolution media, and h is the aqueous diffusion layer or stagnant liquid film layer thickness.

From this relationship, we observe that the particle dissolution rate (*dM/dt* or *dC/dt*) is directly proportional to one parameter that formulators can easily manipulate: the surface area of the solid, *S*. Therefore, if particle size is reduced and the primary particles are well dispersed and wetted, the dissolution rate will increase (surface area is proportional to 1/r, where r is the particle radius, for a constant mass). Particle size reduction and preparation of amorphous solid dispersions are both typical formulation approaches used to increase the dissolution rate of poorly-soluble drugs. However, the concentration of drug in solution will always be limited by the solubility of the drug in the media. By design, inhaled products contain active drug particles smaller than 5 microns in order to be effectively deposited in the airways, and are generally prepared through micronization and lactose blends, and/or spray drying for solids or nebulization for liquids. Therefore, drugs delivered by the pulmonary route typically have a much smaller particle size and higher surface area than their oral counterparts.

Another critical factor impacting dissolution rate is the concentration gradient across the aqueous diffusion layer, *h*. This gradient is the driving force for dissolution and can be adjusted in *in vitro* dissolution testing. The greater the concentration differences between the saturated solubility of the drug and the bulk solution, the greater the dissolution rate of the solid. *In vitro*, we can maximize the dissolution capacity with the addition of surfactants to enhance wetting of particle surfaces and/or increase the stir or flow rate in a USP dissolution apparatus—but does this reflect the *in vivo* situation?

Another impact on dissolution is the dose to fluid-volume ratio. In the lung, if the volume of fluid is insufficient to fully dissolve the entire drug dose and hydrodynamics in the lung fluid are minimal, the dissolution rate will be slowed due to non-sink conditions (e.g., concentration of drug in solution > 0.1 x drug solubility). Regardless of the solid-state form of the inhaled product, the result can be a prolonged drug release due to a depot effect and/or mechanical clearance of the undissolved drug by simply dosing at a level that inhibits complete dissolution of the active pharmaceutical ingredient.

Based on the information provided above, the volume and composition of dissolution media, the drug dose, particle size and solubility in the media are all parameters that impact dissolution rate and the amount of drug potentially available for absorption over time. Therefore, for pulmonary products, at a minimum, we need to understand the characteristics and volume of lung fluid available for dissolution throughout the various regions of the lung, as well as the hydrodynamics and the residence time in the lung, in order to better understand and relate *in vitro* dissolution measurements to *in vivo* particle dissolution. Without this knowledge and understanding, our ability to design a science-based pulmonary dissolution test method that reflects product bioperformance will be hindered.

Drug dissolution in the lung

Lung fluid

The lung is composed of a network of airways known as the upper conducting zone and the lower respiratory zone. The surface area associated with the upper conducting zone is approximately 1-2.5 square meters, while that of the respiratory zone is approximately 100-140 square meters.[8-9] The total amount of "fluid" in a healthy lung is reported to be between 10-70 mL in humans.[10] The composition of the fluid in the two zones varies significantly and therefore, the fluid in the lung available for dissolution is by no means homogeneous. Since the lung fluid is spread out over a large surface area, it is more like a film than a bulk solution. In the simplest case, using the estimates for total fluid volume and surface area of the lung, on average, the lung surface is covered with approximately 0.07 to 0.7 mL of "fluid" per square meter of total surface. As is discussed in the next paragraph, even this is an over simplification because the "fluid" is not distributed evenly throughout the lung.

In healthy humans, the upper airways contain approximately 10-30 mL of a viscous, highly cross-linked, mucus fluid layer, covering basal, goblet, brush and ciliated cells.[11] The mucus is composed of approximately 95% water and a 5% mixture of inorganic salts, mucin, protein and lipids.[12] The mucus layer serves as both a physical barrier to particle diffusion and a defense mechanism for the lung. Reported values for thickness of the mucus-rich layer varies by location in the airways and, based on various reports, decreases from approximately 15 microns in the upper conducting airways to 3 microns in the lower conducting airways. In patients, as anticipated, disease can impact the viscosity, composition and thickness of the mucus layer. Smokers and patients with chronic bronchitis, cystic fibrosis or COPD have mucus layers differing from those of healthy subjects.[13] In contrast, the liquid in the respiratory zone, containing the alveoli, is a very thin (0.07 micron), low viscosity layer of lung surfactant covering Type I (~93%), Type II (~7%) and basal cells.[9,12] The alveolar region contains approximately 7-20 mL of lung surfactant and does not contain a mucus barrier layer or cilia.[9]

Clearance mechanisms and residence time

Drug particles that are deposited in the upper airways may not initially dissolve but become suspended in the mucus layer or bound to the negatively-charged mucins.[14] Undissolved particles can be cleared by mucociliary clearance (MCC) (equivalent to the gastrointestinal tract (GIT) peristaltic housekeeping wave) before they have an opportunity to dissolve. If dissolution does occur, diffusion of the dissolved drug through the viscous, cross-linked mucus layer slows the drug transport. The reported rate of mucociliary clearance from the airways varies by researcher, disease state, patient, particle size, solubility and the salinity of the formulation inhaled. The MCC values in healthy subjects and asthmatics were determined to be 40% per hour for nebulized isotonic solutions.[15] Therefore, within approximately 2.5 hours, undissolved particles can be cleared from the ciliated airways. By comparison, clearance from the deepest regions of the lungs, where the smallest particles deposit, can take from 12 up to 24 hours.[16] Undissolved particles that deposit in or migrate to the alveolar region and are engulfed by macrophages can be sequestered there for years.[11] Particles that are dissolved in the surfactant layer can avoid being engulfed and cleared by macrophages; however, it is not understood whether engulfed particles can continue to dissolve within these macrophages.

In summary, for inhaled, topically-active drugs, the ability to reach the site of action is dictated by the ability of the drug to dissolve in the lung fluid layer and diffuse to the site of action. Factors affecting these processes include the amount of drug deposited, as well as the location, solubility and mobility of the drug in the regionally-diverse lung lining fluids, the particle deposition patterns, drug binding, permeability of the drug and residence time in the lung.

A dissolution comparison: The lung is a bucket and the GIT is a tube

The main contributor to transit or clearance within the gastrointestinal tract (GIT) is the peristaltic housekeeping wave, which moves orally-ingested materials along the alimentary canal. The analogous clearance mechanisms of the lung are mucociliary clearance in the airways and macrophages in the alveoli. However, for the lung, the mechanism encountered will be dependent upon the site of drug deposition, drug dose, drug solubility in the local lung fluid layer, physical size and complexation. Therefore, the residence time in the lung can vary from 1 hour to 24 hours.[17] In the GIT, clearance is generally impacted by metabolism, peristaltic motion, fed- or fasted-state of the individual and time of dosing. GI transit through the small intestines (the site of most oral absorption) is on the order of 199 minutes.[18] As discussed previously, the liquid in the lung exists as a film consisting of viscous mucus in the airways and a thin layer of lung surfactant in the alveoli. The average amount of bulk fluid in the stomach is 500 mL.[19] Therefore, the total volume of fluid in the lung is less than that in the GIT and exists as a film. The pH varies much more dramatically in the GIT compared to the lung.[20] Also, the dose to the lung is dependent upon aerodynamic particle size, the delivery device, patient and deposition pattern. The

dose delivered to the lung is always less than the amount in the individual dosage unit and will vary depending upon the choice of delivery technology and compliance by the patient. For oral medications, the dose is the amount of drug in the individual dosage unit. The site of action for most inhaled drugs is local, while that for most orally-administered drugs is systemic. A comparison of these properties for the oral and pulmonary routes is provided in Table 1.

Table 1

Properties of Oral and Pulmonary Products/Routes in Healthy Humans

Property	GIT	Lung
Typical site of action	Systemic	Local
Transit time	199 minutes (mean intestinal transit time)	1-24 hours
"Fluid" volume	50-1,100 mL Average: 500 mL	10-70 mL
"Fluid" properties	Bulk liquid Location-specific pH	Surface fluid layers Location-specific viscosity, composition and thickness
pH Range*	Range: 1.4-7.4 Stomach: 1.4-2.1 Duodenum: 4.4-6.6 Ileum: 6.5-7.4	6.69 ± 0.07[26]

*Fasted state

Is drug dissolution biorelevant for inhaled drugs?

As noted, there are many differences between the *in vivo* environment that orally-administered drugs encounter compared to inhaled drugs. Both routes of administration are admittedly complex. Is there an opportunity to gain a better understanding of the effectiveness of inhaled drugs using *in vitro* data? Of course there is. However, the understanding we seek may not be achieved by prescribing *in vitro* dissolution testing for all inhaled drug products. From a physicochemical perspective, it has been demonstrated that the role of excipients and solid state of the formulation and drug substance can impact the *in vitro* rate of dissolution of poorly-soluble compounds when delivered from pressurized metered dose inhalers.[21,22] Dissolution testing of inhaled drugs may indeed confirm that the drug particles are sufficiently small, well-dispersed and wetted for dissolution to occur over a specified period of time in an *in vitro* setting. But given the deposition and regional complexity of the lung biology and the residence time, are the data biorelevant? For inhaled products, there are unique and standardized *in vitro* test methods in place that accurately measure the dose as well as the aerodynamic particle size, which provide data suggestive of the distribution of inhalation drugs in the lung. Are these test methods, which are unique to pulmonary products, inadequate to control the quality of all inhaled drugs?

Perhaps a better approach to understanding a link between critical quality attributes and product bioperformance of pulmonary products can be found in the approach developed by Amidon and coworkers in 1995.[23] Their approach, the Biopharmaceutical Classification System (BCS), is a science-based approach used for classifying orally-administered drugs. Using three simple, data-derived numbers that take into account the dissolution, dose and absorption for a particular drug substance, one can determine if a drug will be solubility-limited or permeability-limited. The development and utilization of the BCS system over the past 20+ years has resulted in an improved Scale-Up and Post-Approval Changes Guidance for Immediate Release Products (SUPAC-IR) from the United States Food and Drug Administration (FDA), a dissolution guidance, and an FDA guidance on waiver of *in vivo* bioequivalence studies for drugs administered as solid oral-dosage forms.[24] Over the years, the oral classification system has continued to be refined as further research and understanding of oral drug physicochemical properties are linked to oral bioavailability and delivery.[25]

Can a biopharmaceutical classification system with as much promise be developed for inhaled drugs? At least one paper has been published on this topic.[12] However, there are many key and critical attributes of the lung that are unknown and so dissimilar to the oral route of administration that it would not be possible to map the oral BCS system attributes of solubility and permeability directly to a system for an inhalation BCS (iBCS). For instance, dissolution in the lung may or may not be a critical parameter for pulmonary drugs, due to the lack of free-flowing, low viscosity fluid and long residence time (recall that the lung is "a bucket"). Absorption may not be relevant for topically-active, inhaled drugs that are not intended for systemic administration. However, as we know, systemic blood levels are typically required to establish IVIVC relationships for other routes of administration. It is true that *in vitro* dissolution testing is in place for other administration routes and the pulmonary route appears to be the exception. It is also true that a link between *in vitro* dissolution data and systemic blood levels generated for products delivered by non-pulmonary routes of administration form the basis for establishing IVIVCs. However, implementation of additional *in vitro* testing should be science-based and linked to critical quality attributes. The vast majority of inhalation products are locally active, not systemically active, and in fact, systemic exposure

may be an unwanted attribute for many of these drugs. From a scientific perspective, it makes more sense to start with the task of developing a classification system for inhalation products that would identify gaps in quality attributes than to design and implement testing apparatuses and procedures that may not be biorelevant and only add to the cost of product development.

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Jayne E. Hastedt is Managing Director, JDP Pharma Consulting, LLC, P.O. Box 1127, San Carlos, CA 94070, +1 650 534-4062, jayne@jdppharma.com. Website: www.jdppharma.com.