

# More predictive power in pharmacokinetics

## Summary

Developing inhaled medicines is often slowed by the difficulty of predicting how drugs dissolve in the lungs and enter the bloodstream. Traditional *in vitro* and animal models rarely capture the complexity of human lung physiology, creating uncertainty and risk in formulation and regulatory approval.

DissolvIt® provides an innovative solution: an *in vitro* method that simulates the integrated pulmonary dissolution and absorption in a physiologically relevant system. By replicating the lung's air–blood barrier, using realistic fluid volumes, and mimicking epithelial diffusion, data are generated that closely align with pharmacokinetic outcomes observed in patients.

Evaluated in a study funded and monitored by the U.S. Food and Drug Administration (FDA), DissolvIt® enables earlier identification of formulation challenges, reduces the need for animal studies, and makes faster development cycles possible. A key differentiator is the richness of the data it delivers compared to conventional methods – a benefit that has already proven highly relevant to customers. DissolvIt® offers industry a trusted pathway to accelerate safe, and effective inhaled therapies.

The core value DissolvIt® delivers more predictive power in pharmacokinetics – reducing the likelihood of costly failures in later development by providing precise, clinically aligned data early in the process.

## Introduction: Why Dissolution Matters

The journey of an inhaled drug from the inhaler into the bloodstream differs from drug to drug. A crucial step once the drug particles reach and deposit in the lungs is dissolution—the process of a solid drug dissolving in lung fluid then crossing the epithelial cell layer and entering the systemic circulation. If the real lung dissolution deviates too much from early theoretical estimates—either relating to the therapeutic targets of a new drug or to the dissolution of generic candidates vs an original brand—therapeutic efficacy or bioequivalence can be compromised. Therefore, regulatory agencies increasingly recommend dissolution testing to support formulation design and quality control.

Predicting this process is an essential part of preclinical research. At this time, there is no universally accepted “gold standard” method for studying the dissolution of drugs intended for inhalation. Existing approaches have provided first valuable insights but remain constrained by poor predictability of inhalation pharmacokinetics in the clinic. A long-standing objective in the field is therefore to establish an in vitro system that more closely resembles the properties of the human lung, as to provide a smaller translational gap to be bridged by the associated PK modeling efforts. Such a system would enable researchers to detect small deviations between different inhalation formulations, providing a foundation for selecting the most promising drug- or formulation candidates early in development before any clinical data has been collected, leading to greatly decreased costs if these early conclusions prove to be correct.

The ultimate goal is to accurately predict clinical outcomes and in-patient data. This involves translating the in vitro dissolution data through modeling and simulation, to better simulate the systemic PK curve following inhalation exposures in the clinic. The development and regulatory acceptance of such an approach, enabling substantially improved in vitro–in vivo correlations (IVIVC) for inhaled products, would represent a major step forward for the field.

Recognizing the need for more sensitive in vitro methods, FDA supported an evaluation of DissolvIt® as a potential tool to better detect the potential effect of small formulation differences on dissolution and absorption early in development.

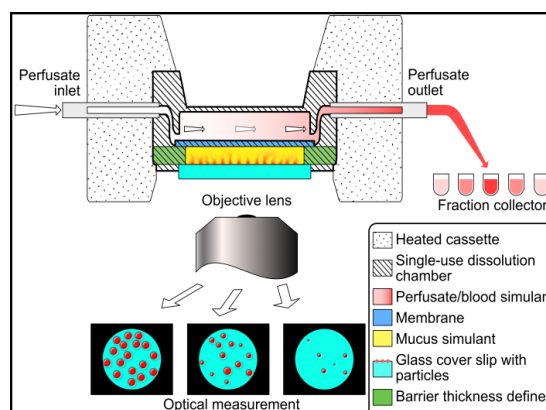
## DissolvIt®: A New Approach

DissolvIt® is an in vitro dissolution and absorption test method specifically designed for inhaled drug products. DissolvIt® mimics the air–blood barrier of the lungs by combining:

- A controlled air–liquid interface, replicating the respiratory tract surface.
- A simulated pulmonary fluid environment, reflecting the rapid passage of small fluid volumes past the model mucosa in a single-pass mode and onto a fraction collector.
- An absorptive compartment, modeling the epithelial transport of dissolved drug into systemic circulation.

By integrating dissolution and absorption in a single system, DissolvIt® provides pharmacokinetically relevant data such as C<sub>max</sub> and T<sub>max</sub> as well as the fraction of an inhaled drug that is likely to reach systemic circulation over time after inhalation.

**A schematic view of the DissolvIt® module >**



# Advantages of DissolvIt®

## 1. More Predictive Power in Pharmacokinetics

DissolvIt® provides more predictive power in pharmacokinetics by generating dissolution and absorption data that closely resemble in vivo outcomes, including maximum plasma concentration (C<sub>max</sub>) and time to maximum concentration (T<sub>max</sub>). No other in vitro system currently provides this type of clinically relevant primary data. DissolvIt® also generates cumulative dissolution profiles over time, similar to conventional methods, but with the added advantage of direct PK relevance.

DissolvIt® provides mechanistic clarity: distinguishing whether poor systemic exposure is due to either slow dissolution in lung fluid or to limited absorption across the pulmonary epithelium. This insight directly provides data for formulation strategies such as particle engineering, solubilization technologies, or excipient selection.

## 2. Differentiation from Conventional Models

Unlike conventional in vitro dissolution methods, which often fail to provide clinically predictive data, DissolvIt® delivers sharper insights that align more closely with patient outcomes. This predictive power enables companies to make go/no-go decisions earlier and with greater confidence, avoiding the risk of advancing weak candidates into costly clinical phases. Conventional methods that rely on repeated sampling from an agitated fixed volume of perfusate risk providing false limiting dissolution due to saturation and do not generate pharmacokinetic information such as T<sub>max</sub> and C<sub>max</sub>. In contrast, DissolvIt® accurately measures the percentage of the applied dose that is absorbed into the system and has demonstrated the ability to predict clinical outcomes in an FDA-funded study.

## 3. Biorelevance for the Respiratory Tract

The system reproduces essential features of the pulmonary environment, such as an evenly deposited low dose, limited fluid volumes, the distinctive air-liquid interface, presence of lipids in the mucus simulant and albumin in the blood simulant. By capturing these characteristics, DissolvIt® reflects the real challenges faced by inhaled drugs, including solubility-limited absorption and slow dissolution kinetics. The fluids in DissolvIt® (mucus and blood simulant) always have the same composition which enables a direct comparison of derived pharmacokinetic results between all items tested, as opposed to conventional methods where the fluids are altered due to the solubility of the API tested.

## 4. Supported by FDA Collaboration and Guidelines

DissolvIt® was evaluated in a FDA-funded study under an FDA Broad Agency Agreement. The FDA monitored the work and approved publication — a strong signal of scientific credibility and external affirmation. This collaboration coincides with new FDA product specific guidelines which explicitly recommend dissolution testing for evaluating and characterizing inhaled drug products. DissolvIt® is not just innovative, it is aligned with the direction regulators themselves are taking.

## 5. Reduction of animal use and clinical trials

DissolvIt® helps reduce reliance on exploratory animal testing and supports refinement of clinical trial design. By providing predictive pharmacokinetic data earlier, DissolvIt® directly supports the 3Rs principle (Replace, Reduce, Refine) – an increasingly important regulatory and ethical requirement in drug development.

## Limitations and Realism

No in vitro dissolution method can fully replicate the complexity of the human lung, with its dynamic airflow, low dose per area unit, regional deposition, immune interactions, and metabolism. DissolvIt® does not capture active transport or metabolic processes in lung tissues. However, it provides a physiologically faithful, regulator-recognized bridge between simple static dissolution tests and costly in vivo studies.

## Conclusion and Outlook

DissolvIt® represents a major advance in inhalation drug development by integrating pulmonary dissolution and absorption in a physiologically relevant model, offering more predictive power in pharmacokinetics than any other in vitro method.

Its advantages include:

- Detects differences in dissolution originating from small formulation variations e.g. excipients, particle size and manufacturing method.
- Generates detailed dissolution data with high resolution including Cmax and Tmax, for both fast and slowly dissolving substances.
- Improved prediction of pharmacokinetic properties for new chemical entities and generics.
- Identifies and ranks candidate drugs vs. their originators.
- Supports reduction of animal testing (3R).

Above all, the platform stands out for the richness of the data it provides – a unique differentiator.

DissolvIt® helps companies de-risk inhaled drug development by delivering sharper, more predictive data early in the R&D process. This leads to fewer clinical trial failures, faster go/no-go decisions, and more efficient use of R&D resources.

To receive updates or access detailed findings as they are released, we invite you to connect with us at Inhalation Sciences.



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