Pion

APPLICATION NOTE

3 BENEFITS OF CONDUCTING SIMULTANEOUS DISSOLUTION AND PERMEABILITY TESTS

A Single MicroFlux Apparatus

On the left side is the donor compartment where the sample is positioned, and dissolution is monitored in real-time with a UV/Vis fiber optic probe. On the right is the acceptor compartment with an additional fiber optic probe to measure the absorbed API concentration. The two compartments are separated by a membrane coated with a validated phospholipid mixture which, in combination with a proprietary buffer in the acceptor compartment, creates conditions that mimic the human jejunum in the gastrointestinal (GI) tract. This unique setup allows acquisition of complete profiles that assess simultaneous dissolution and membrane permeability.

Running a simultaneous experiment for both solubility/dissolution and permeability is a powerful approach to better understand the potential absorption effect of solubilizing agents.

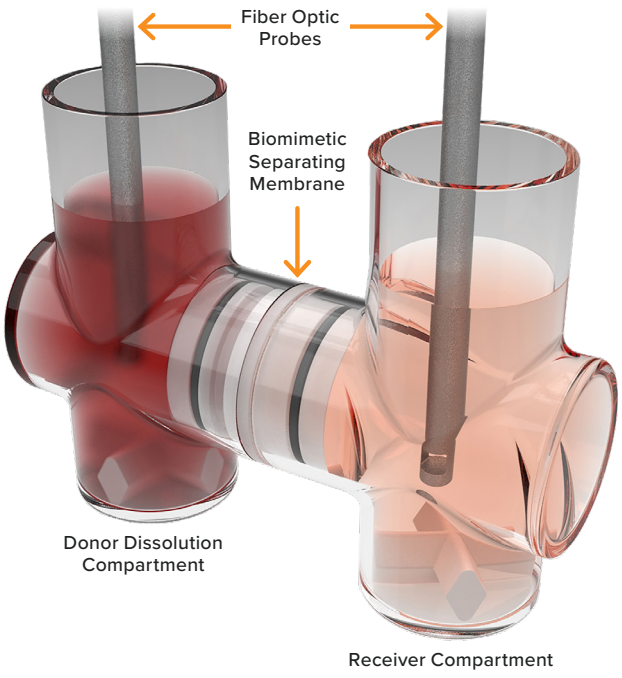


Figure 1. A Flux chamber consists of two chambers separated by a biomimetic membrane to combine dissolution and permeability tests in a single experiment.

Figure 2 shows the results of a simultaneous dissolution-permeation assay comparing unformulated and formulated API. On the donor side, the dissolution profile of the formulated product looks advantageous, but the concentration profile in the acceptor compartment shows that the formulation causes a significant decrease in membrane permeability, such that the unformulated API outperforms the formulated one in the acceptor compartment.

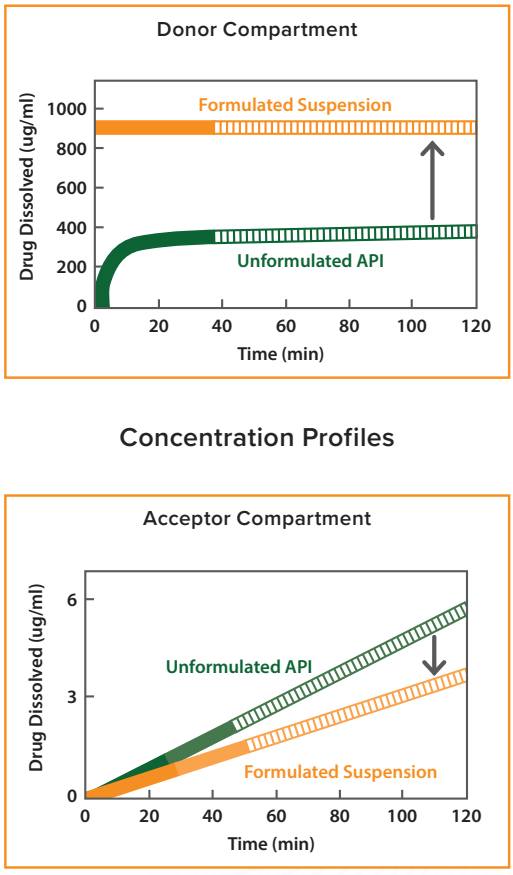


Fig 2. Comparison of formulated and unformulated API in a dissolution-permeation (flux) assay. The unformulated API provides higher concentration profile (flux) in the acceptor compartment due to significant membrane permeability decrease caused by the formulation excipient matrix.

Here's a breakdown of the 3 main benefits of combining the two assays:

Enhanced Efficiency and Throughput

- **Reduced Sample Requirements:** Testing of dissolution and permeation in a small volume apparatus can reduce the amounts of drug substance and excipient needed, which is especially beneficial when dealing with limited quantities of new chemical entities (NCE's) or low-dose/high-potency drugs.
- **Streamlined Workflow:** The combined setup simplifies the experimental procedure and data analysis, making the overall process more efficient.
- **Formulation Ranking and Selection:** Simultaneous tests can be used to rapidly rank different formulations based on their dissolution and permeation characteristics. This helps in selecting or rank ordering the most promising formulations for further development.

Better Formulation Development and Optimization

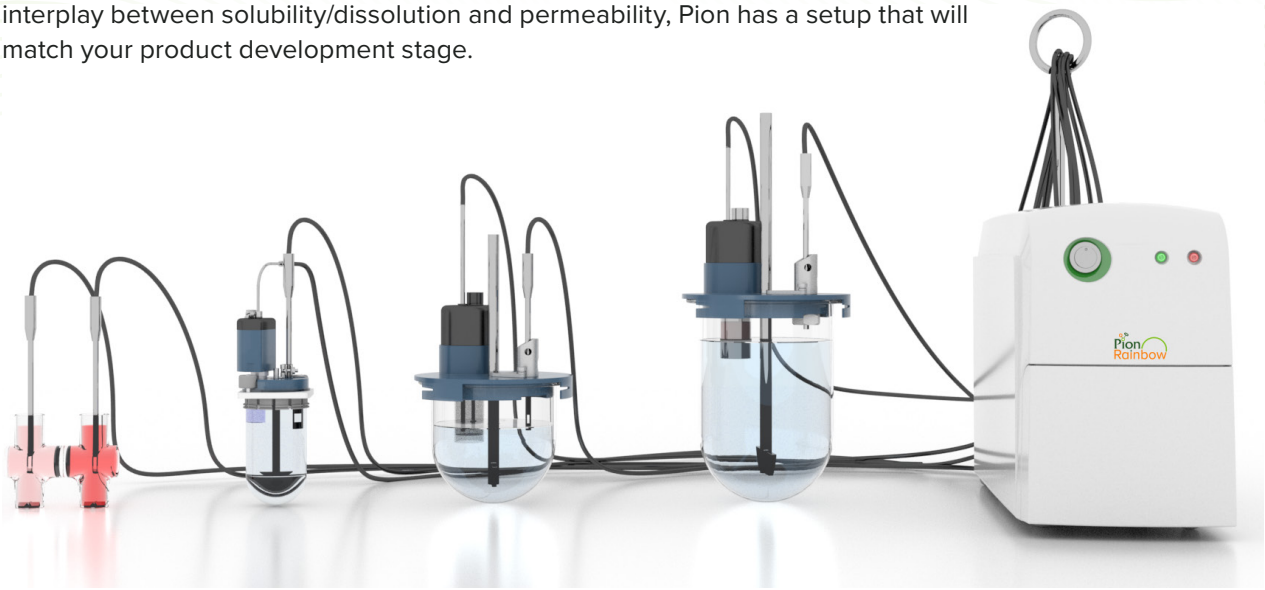
- **Derisked Formulations:** Improve the likelihood of formulations passing animal or human tests.
- ***In Vitro-In Vivo* Correlation (IVIVC):** The data generated from simultaneous dissolution-permeation tests combined with *in silico* mechanistic modeling by Predictor™ can be used to develop robust *in vitro-in vivo* correlations. A stronger IVIVC allows for better assessment of in vivo performance based on *in vitro* data, reducing the need for extensive animal studies.
- **Mechanism Elucidation:** The combined approach of *in vitro* testing and mechanistic modeling can provide insights into the mechanisms of drug absorption and the impact of excipients on the process. For example, it can help determine whether dissolution, solubility or permeability is the rate-limiting step in the absorption process.

Regulatory Advantages

- **Biowaivers:** In certain cases, a strong IVIVC established using simultaneous dissolution- permeation data may support a biowaiver for bioequivalence studies, reducing the need for human clinical trials.
- **Justification for Formulation Changes:** During post-approval changes to a drug product, simultaneous tests can be used to demonstrate that the changes do not significantly affect drug release and absorption potential.

Possibilities

Wherever you are in the development process, whether it is drug discovery, pre-formulation, formulation or bioequivalence assessment, there is a flux setup available to meet your needs. Options range from small-scale testing when API is limited to larger, biorelevant volumes for later stage studies. When you're ready to assess the interplay between solubility/dissolution and permeability, Pion has a setup that will match your product development stage.



Pion offers a number of different flux setups to match your volume requirements

In Vitro + In Silico

When *in vitro* dissolution-permeation (flux) assays are paired with an *in silico* model that expands the *in vitro* experiment conditions to the real physiological characteristics of the GIT with potential particle drifting effect of the formulations, you gain a better understanding of the parameters that will modify/improve the *in vivo* absorption characteristics of your formulations. Pion's Predictor platform provides in vivo effective permeability and absorption rate predictions based on a mechanistic modeling approach applied directly on the dissolution-permeation data. The software can also predict the rate limiting step of absorption, further aiding the decision making of the formulators.

This approach can accelerate formulation development, improve *in vivo* predictions, and reduce the amount of animal studies.

By employing this system, formulators may elucidate the interplay between dissolution and permeability, making rational decisions intended to enhance drug absorption for their formulations.

CONTACT OUR SCIENTISTS TO LEARN MORE

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