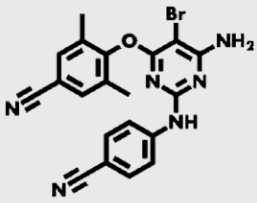
CASE STUDY

De-risking Formulation Development: Using the MacroFLUX System to Predict Human Outcomes of KinetiSol Processed Etravirine

Co-authored by Daniel Davis, Ph.D., PharmD, Director of Business Development at Austin PX

AustinPx, a contract development and manufacturing organization specializing in oral solid dosage forms, undertook the development of a generic formulation of etravirine (marketed under the brand name Intelence®), a non-nucleoside reverse transcriptase inhibitor (NNRTI) for HIV therapy. Etravirine is classified as a BCS Class IV compound, characterized by low solubility and low permeability, and it is prone to rapid recrystallization.



etravirine

Formulation Challenge

The intrinsic properties of etravirine posed multiple technical challenges. The API exhibits poor aqueous solubility, limited intestinal permeability, and susceptibility to thermal degradation at ~210 °C, which is below its melting point of ~260 °C. These factors complicate both formulation and manufacturing as hot melt extrusion is impractical due to thermal sensitivity, while spray drying requires precise control over particle morphology to reproduce supersaturation and dissolution kinetics.

In addition, etravirine displays a pronounced food effect, with exposure increasing approximately six-fold in the fed state compared to fasted conditions. For generic development, regulatory standards required matching the reference product's pharmacokinetic profile in both states. Achieving consistent *in vivo* performance required careful formulation optimization and a predictive in vitro tool that could distinguish bioavailable drug from total dissolved drug, particularly given the compound's tendency to form colloidal aggregates.

KinetiSol ASD as a Solution Platform

AustinPx applied their KinetiSol processing to produce amorphous solid dispersions (ASDs) of etravirine. KinetiSol is a high-shear, fusion-based technology that generates amorphous dispersions through frictional heating without requiring the API to reach its melting point (Figure 1).

This approach allowed processing within a narrower thermal window, avoiding thermal degradation while achieving full amorphization. KinetiSol also offers flexibility in excipient selection and particle design, expanding the formulation design space compared to traditional spray drying or hot melt extrusion.

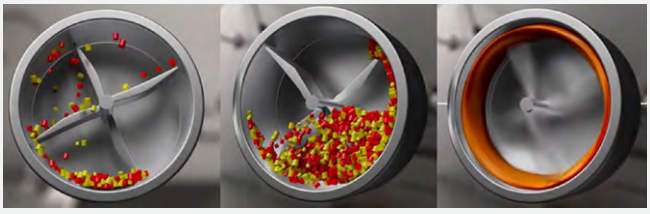


Figure 1. Austin PX KinetiSol Processing

Despite achieving amorphization, standard dissolution testing under sink conditions failed to reliably predict *in vivo* exposure. While traditional dissolution measurements indicated rapid dissolution for both the reference spray-dried product and the KinetiSol formulations, subsequent *in vivo* pharmacokinetic studies revealed significant discrepancies. These findings highlighted a fundamental limitation: measuring total dissolved drug did not account for the fraction available for permeation, particularly in a compound prone to colloid formation.

Application of the MacroFLUX™ System for Predictive Testing

To address this challenge, AustinPx integrated the MacroFLUX system (Figure 2) into their development workflow. The system adds a second, lipid-coated acceptor compartment to standard dissolution measurements. While the donor compartment quantifies total dissolved drug, the acceptor compartment measures drug flux across a biomimetic membrane, providing an estimate of the free, absorbable fraction.

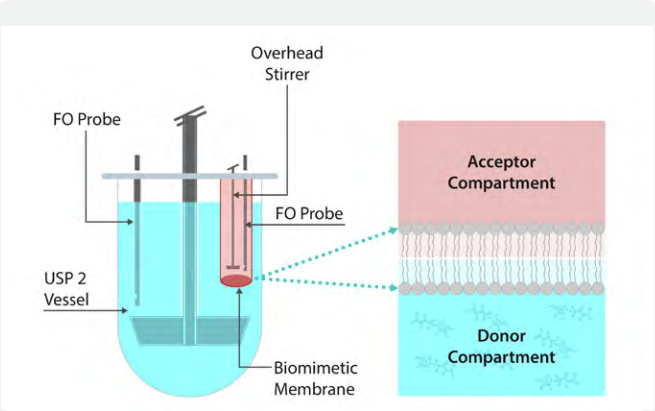


Figure 2. Schematic of the MacroFLUX dissolution-permeation apparatus.

Use of the MacroFLUX system enabled several key insights:

1. **Discrimination between formulations** – Acceptor measurements revealed differences in drug flux not apparent from dissolution data, highlighting which formulations were likely to reproduce the desired human pharmacokinetics.
2. **Correlation with *in vivo* data** – Retrospective comparison demonstrated that acceptor flux data closely aligned with dog and human area under the curve (AUC) values, while dissolution data alone was misleading.
3. **Formulation iteration** – Using acceptor measurements, formulation parameters were systematically varied, including particle size (milling speed), injection temperature, and solubilization agent concentration. Changes in the concentration of the solubilizing agent sodium stearyl fumarate (SSF) had the largest effect; reducing the concentration from 1% to 0.5% significantly increased acceptor flux, improving alignment with the reference product in the fasted state.

By iteratively testing and adjusting formulations using MacroFLUX acceptor data, AustinPx identified a composition that achieved bioequivalence in both fed and fasted states without extensive reliance on *in vivo* studies.

Figure 3 shows the MacroFlux acceptor data for the KinetiSol tablet formulation 30044, containing 1% SSF. This was previously tested in humans and matched the performance of Intelence in the fed state; however, it was found to be inferior in the fasted state. KinetiSol tablet formulation 30061 was tested, containing 0.5% SSF. The MacroFlux acceptor data demonstrated superimposable profiles to the reference product Intelence under fasted state conditions.

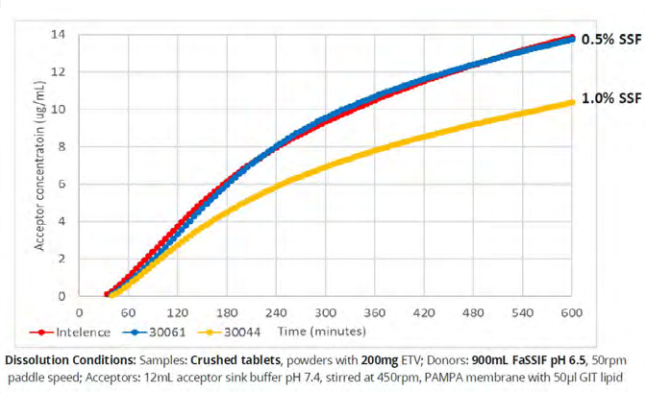


Figure 3. Proposed Formulation Nominated from MacroFlux Testing

KinetiSol formulation DST-9256 (which is equivalent to formulation 30061) was sent for human PK testing. Modifying the SSF amount from 1.0% to 0.5% successfully matched to the clinical outcome of Intelence in both the fed and fasted states (Figure 4).

Key Outcomes

- **Fed-state bioequivalence** – Achieved alignment between KinetiSol ASD and the reference spray-dried product (Intelence).
- **Fasted-state bioequivalence** – Formulation adjustments guided by the MacroFLUX acceptor data enabled predictive matching of exposure.
- **Mechanistic insight** – Flux measurements provided insight into supersaturation and precipitation kinetics, distinguishing free drug from non-absorbing colloids.

Conclusion

This project illustrates the utility of integrating mechanistic *in vitro* tools into ASD development for poorly soluble, low-permeability compounds. In the case of etravirine, the MacroFLUX system enabled rational formulation decisions, identifying parameters that directly influenced bioavailable drug flux. Coupled with the KinetiSol process, this approach allowed AustinPx to predict human pharmacokinetics with greater confidence, de-risking clinical studies and enabling efficient development of a generic formulation for a complex BCS Class IV compound.

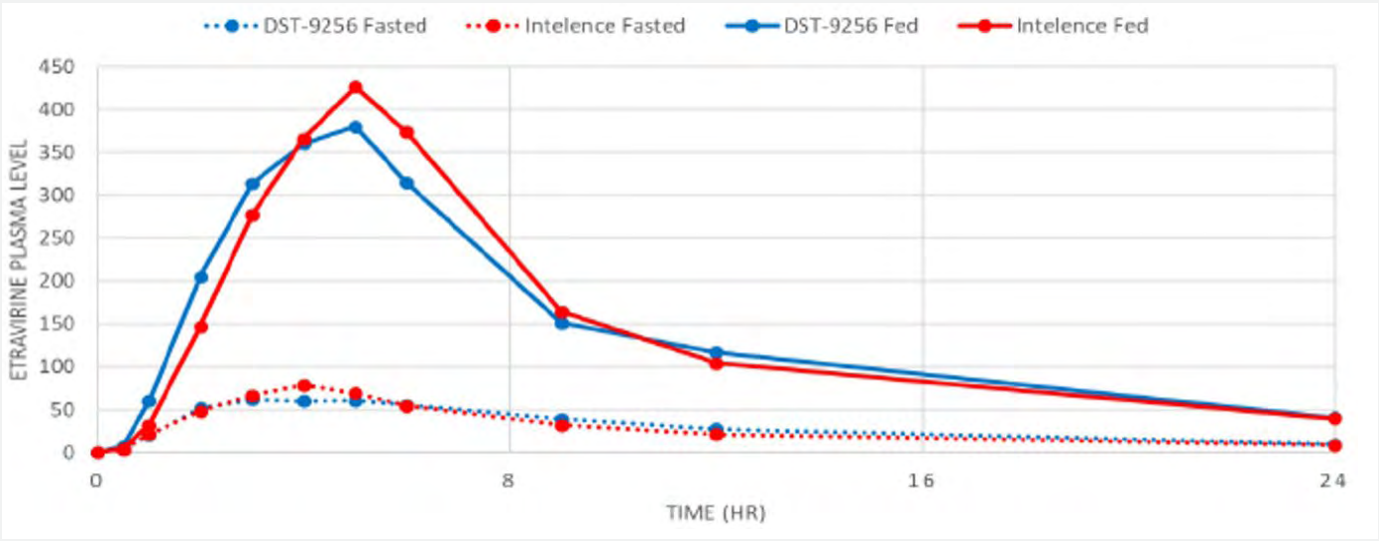


Figure 4. Successful Human PK Match.

Why Use Pion

Pion products accelerate formulation development, helping you save time, reduce costs, and improve outcomes. We know that accurate determination is essential to select the right candidates in order to define the optimal path for drug development.

Pion empowers the pharmaceutical R&D community helping to make important decisions on candidate selection based on trusted data for drug optimization, which will impact people's lives. In other words, we help scientists to find the right answers faster to select the best strategy for a successful drug.