

Simcyp *In Vitro* (Data) Analysis (SIVA) Toolkit:

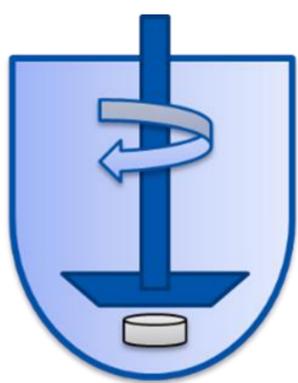
Deciphering Dissolution Experiments and Translating Intrinsic Parameters into PBPK models

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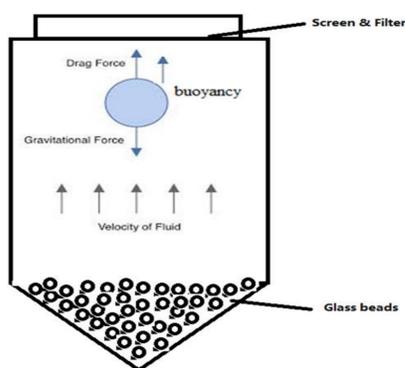
INTRODUCTION: *In vitro* dissolution is a critical component of drug product development programs and is often used as a potential surrogate for *in vivo* performance. For non-BCS 1 API the direct transfer of *in vitro* dissolution profiles to *in vivo* simulations can be misleading. Mechanistic dissolution models enable the dissolution environment (pH, flow rates, fluid volumes *etc.*) to be accounted for thus enabling *in vitro* and *in vivo* differences (including population variability) to be considered. With this principle in mind we are developing modelling tools to assess mechanistic model performance on *in vitro* experiments and, if required, estimate unknown or uncertain parameters (dissolution and precipitation).

The SIVA Toolkit is a user-friendly module, designed to assist pharmaceutical scientists with analysis of data generated from *in vitro* experiments -USP II, USP IV, Serial Dilution, Transfer Models, Two Phase Dissolution Models. The Toolkit permits the evaluation of mechanistic model performance; IF required, parameter estimation tools can be used to refine/estimate uncertain/unknown parameters (e.g., PSD) or to estimate global correction scalars. Once satisfied with the *in vitro* model, (estimated) parameters can be used in *in vivo* simulations using PBPK models.



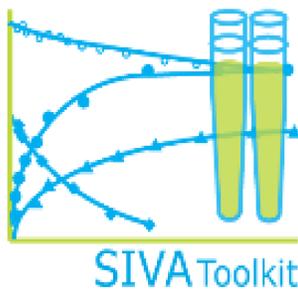
USP- II Dissolution Experiments (SIVA v1)

- Simultaneous modelling in different Media
- Different Paddle RPM & Fluid Flow Dynamics
- Accounts for buffer capacity / particle surface pH
- *Modelling Disintegration of the formulation*
- See accompanying poster for example (Liu *et al.*)

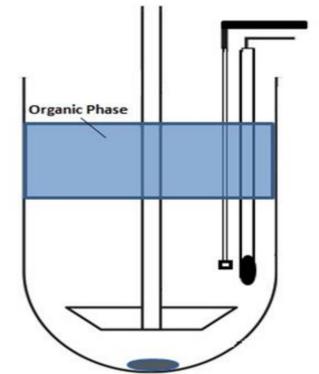


USP- IV Dissolution Experiments (SIVA v2)

- Open and Closed System Experiments
- Dual Model Structure for Particle Motion
 1. Following System,
 2. Holding System
- Media change during the experiment
- Flow Rate, Flow cell size, Pump frequency as input options

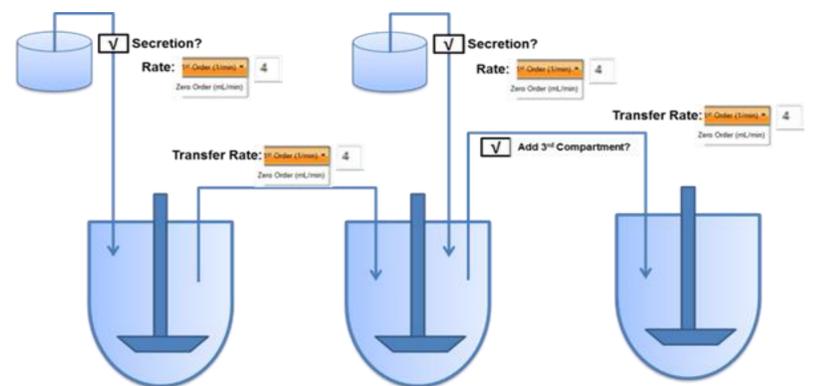


REFINED PARAMETERS



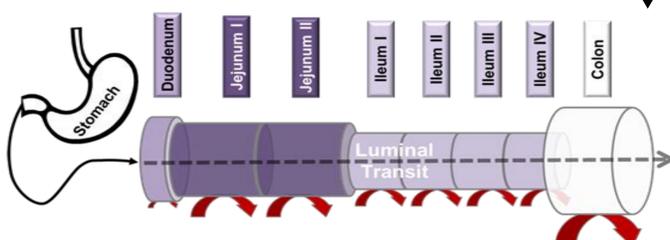
Two Phase Dissolution Experiments (SIVA v2)

- Simultaneous monitoring aqueous & organic phase
- Aqueous media change during the experiment
- Precipitation/Supersaturation parameter estimation
- Ability to simulate modified release formulations

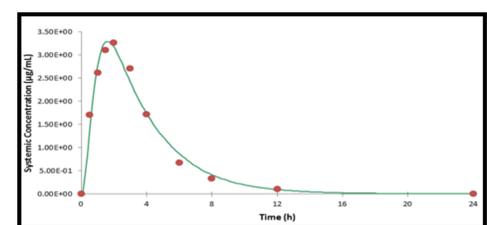


Transfer Experiments (SIVA v2)

- Flexibility in defining number of compartments
- Specify transfer rates and secretion rates (optional)
- Dynamic pH and surfactant changes with time
- Flexibility in defining fluid volumes, paddle speed



Improved
PK Predictions



The SIVA toolkit offers a variety of mechanistic modelling tools designed to derive useful information from *in vitro* dissolution/precipitation experiments that can be used to inform *in vivo* modelling within a PBPK environment. We are collaborating with OrBITO partners (a side-ground project) to evaluate this approach with a range of different API.