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

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

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.