Introduction

- Advanced application of commercial PBPK software can be restricted because users do not have access to the source code.
- Thus, the built-in models or individualised physiological parameters cannot be modified albeit that alternative models can be selected via screen options.
- For example, the gastric emptying function within absorption PBPK modelling framework is usually modelled as a first order process.
- However, gastric emptying of solids and liquids can have biphasic or more complex patterns; e.g., for solids there may be a lag phase during which little emptying occurs, followed by a linear (zero order) emptying phase, that is independent of gastric volume.
- Simcyp version 17.1 however now provides an interface facility for users to customise in-built ADAM models and parameters.

Customised ADAM Functions

- The interface language used for customising ADAM functions is Lua. Lua together with its interpreter/compiler is very lightweight and flexible, so can easily be embedded in other programs.

Applications

- Fig. 3. Individual fasted pH in gastric aspirates vs. time in the presence of dissolved diclofenac sodium (van den Abeele et al. 2015).
  - Recently, van den Abeele et al. explored gastrointestinal dissolution, supersaturation and precipitation of the acidic drug diclofenac in humans.
  - A 50 mg potassium diclofenac tablet was administered and gastric fluids were aspirated at intervals & dissolved and total diclofenac and pH (Fig. 3) measured.
  - The current default luminal fasted pH function within the simulator is static - pH cannot change as a function of time (Fig. 4).

- Fig 4. Default Static pH model within Simcyp.
  - Diclofenac is a low pKa (3.8) acid and its solubility is sensitive to the range of pH indicated in Fig. 3 which ranges from 2 units above and below the pKa. Thus, it is useful to be able to assess the likely impact on simulation outcomes of dynamic rather than static pH.
  - ADAM Lua interface can be used to intervene in the current static pH model and dynamic time-dependent pH profiles can be simulated in V17.1 (Fig. 2).
  - Although the availability of luminal pH data is rare, the Lua interface can be used to study the impact of acid regulating agents (ARAs) on co-administered drugs; gastric pH profiles of commonly used ARAs at therapeutic doses have been reported.
  - Lua interface together with the PD module has been used to model pH-feedback with a PPI (see Poster Rose et al.).
  - Currently Lua interface can be used to access or intervene in a number of ADAM model functions across all GI-compartments including: a) GI-Luminal pH; b) Fluid rate (volume) (i.e., gastric emptying); c) Drug mass dissolved; d) Drug mass undissolved; and e) Absorption rate constant.
  - Additional simulator state variables can be accessed using codes indicated on the Excel Output WS “Ode State Info”.
  - The long term plan is to provide libraries of example scripts.

References

2. www.lua.org