Depending on Feasibility Populate Physiological Databases From Open Sources (Task 4.5)

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Introduction

The fraction of dose absorbed is affected by numerous factors which can be split into drug- and formulation-specific parameters and physiological parameters (the *system*). An integrated approach that considers the interplay between these factors is important for accurate prediction of the rate and extent of oral drug absorption. Physiological parameters (gastric emptying rate, intestinal transit and mobility, gastro-intestinal fluid pH, secretion and reabsorption, intestinal blood flow, bile secretion, enterohepatic recirculation, and intake of food and fluids *etc.*) form an integral component of predictive tools which rely upon extensive databases storing the mean and population variability of such parameters including, where available, their covariation. While such databases have been developed there remain significant gaps some of which will be addressed in this task.

Areas Being Addressed

1. Circadian Variation

Many physiological processes follow circadian rhythms and the processes involved in determining the rate and extent of oral drug absorption are no exception. Gastric emptying rate and hepatic blood flow are known to be reduced significantly in the evening (night) compared to the morning (day) which may have an impact upon the rate and extent of absorption of acid-labile drugs, enteric-coated formulations and drugs with significant gut-wall and hepatic metabolism. Hence, when the GI transit of drug and blood flow to liver and villi reduces at night, the rate at which drug is carried away from first-pass metabolism sites (gut-wall and liver) is lowered leading to higher first pass metabolism at night compared to the day time.

Figs. 1 and 2 indicate the impact (simulated and clinically observed) of circadian variations on the bioavailability and PK parameters respectively of CYP3A4 substrate and BCS/BDDCS Class II drug Nifedipine.

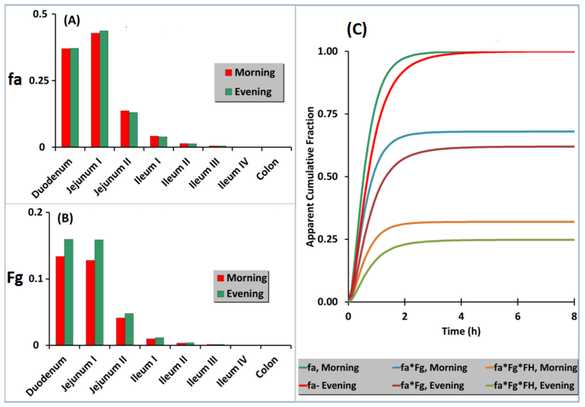

Fig. 1. Morning *vs.* evening regional distribution of (A) fraction of dose absorbed (fa); (B) fraction metabolised (Fg) and, (C) cumulative fa, Fa·Fg and Fa·Fg·F_H profiles for a Nifedipine oral IR dosage form.

A database of circadian variations in the processes influencing oral absorption is to be developed. This will permit the prediction of circadian effects on PK profiles and parameters as well as assisting with exploring different "what if" scenarios before carrying out human studies. Such *a priori* simulations could be very useful especially for narrow therapeutic index drugs which can be affected by circadian variations and help to optimise trial designs or avoid unnecessary clinical studies.

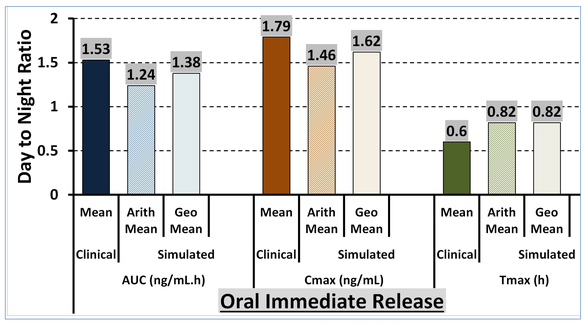

Fig. 2. Day-to-Night ratio of simulated and clinical circadian effect on PK parameters after oral dosing.

2. Viscosity of Physiologically Relevant Dissolution Systems

In order to simulate *in vivo* dissolution and disintegration of drugs, physiologically relevant dissolution media, mimicking gastric or intestinal juices are often employed. For such media, pH, surface tension, ionic strength, osmolality parameters are usually considered. However, little attention has been paid to rheological attributes. The differential viscosity of luminal contents in the fasting and fed states can have a significant impact on dissolution and disintegration of oral dosage forms. The following components will be addressed building this database.

Fasting state condition

Database till date-

- Viscosity in stomach: Chinese and Japanese population
- Viscosity in intestine: Chinese
- Viscosity in colon: Chinese

Further work-

- Viscosity in stomach: Caucasian
- Viscosity in intestine: Japanese and Caucasian
- Viscosity in Colon: Japanese and Caucasian

Fed state condition

Database till date-

- *In vitro* viscosity of FDA breakfast
- *In vivo* viscosity of high viscosity fibres, example.: - Dietary fibres and locust bean gum

Further work-

- *In vivo* viscosity of FDA breakfast
- *In vivo* and *in vitro* viscosity of high and low fat food
- *In vivo* and *in vitro* viscosity of high and low protein food

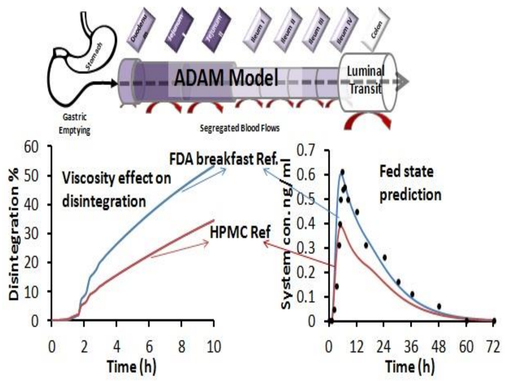

Fig. 3. Trospium chloride case study. Top: schematic of the ADAM model; Bottom: blue/red lines: simulated results for FDA breakfast or HPMC surrogate; blobs-observed plasma concentrations after an FDA standard breakfast.

3. Animal PBPK Models (Beagle Dog, Sprague Dawley Rat, Generic Strain Mouse)

- Studies with preclinical species play an important role in drug development including studies with oral dosage forms. Modelling and simulation tools can, for example, be used to set appropriate dosing levels and to improve/confirm understanding of drug behaviour before moving to human studies. Gastro-intestinal anatomical & physiological data for preclinical species are thus required. Data required include:
- Small intestine and colon anatomy and physiology data (length, diameter, gastric emptying, transit time, pH, bile salt concentrations, villi morphology, unstirred boundary layer).
- Regional small intestine, villus and colon blood flows during fasted and fed state.
- Regional volumes of luminal fluids at steady state (influenced by secretion and re-absorption rates).
- Regional pH and bile salt concentrations in the fasted and fed states.

4. Physiologically Relevant Buffer Systems

Development of dissolution media, closely simulating *in vivo* physiological conditions, is expected to enhance predictions of the *in vivo* performance of test formulations. Bicarbonate buffer plays a major role in the *in vivo* gut but provides significant practical difficulties in *in vitro* dissolution studies. However in terms of the mechanistic modelling and simulation of dissolution in the *in vivo* gut it is necessary to consider the properties of bicarbonate buffer.

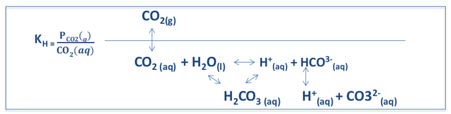

Fig 4. Carbon dioxide/bicarbonate buffer system.

Population data (mean and variability) describing luminal buffer capacity and related intestinal secretion rates of relevant fluids, together with consideration of the effect of food and potentially disease state will be collected. This will then be coupled with mechanistic models for oral absorption prediction, including the modelling of surface (local) pH effects and the dissolution of pH sensitive polymers (enteric-coated formulations).

Task/tasks-

Task 4.5. Depending on feasibility populate physiological database from RIVM and ICRP and any other open sources.

Identified problems/challenges;

Circadian Variations

Manchester University (delayed recruitment)

Viscosity / Buffering Systems –

Looking for contributions / collaborations (data)

Dependencies and collaboration needs;

1. Academic partner Mainz University (Item 2).
2. Academic partner Manchester University (Item 1).

I can continue build on this task;

Yes!

Innovative Tools for Oral Biopharmaceutics