Formulation Predictive Dissolution (fPD) Testing to Advance Oral Drug Product Development: an Introduction to the US FDA Funded '21st Century BA/BE' Project

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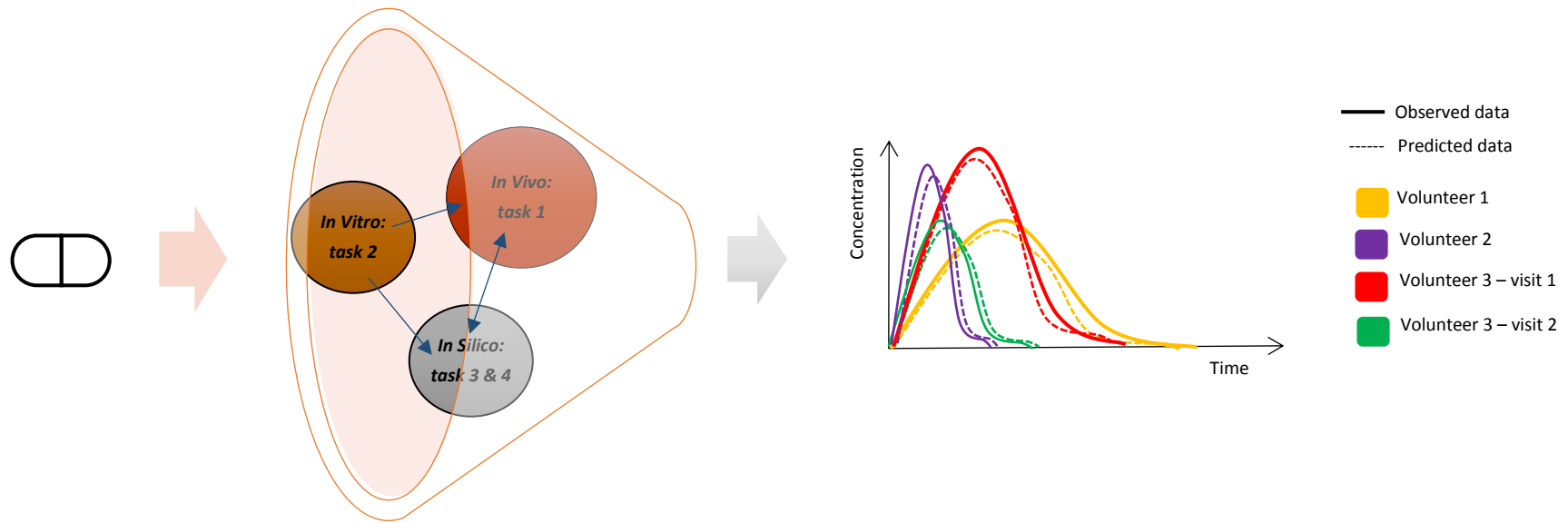
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A New Era for Biorelevant Formulation Predictive Dissolution Testing:

21st Century BE/BA studies

Abstract

Over the past decade, formulation predictive dissolution (fPD) testing has gained increasing attention. Another mindset is pushed forward where scientists in our field are more confident to explore the *in vivo* behavior of an oral drug product by performing predictive *in vitro* dissolution studies. Similarly, there is an increasing interest in the application of modern computational fluid dynamics (CFD) frameworks and high-performance computing platforms to study the local processes underlying absorption within the gastrointestinal (GI) tract. In that way, CFD and computing platforms both can inform future PBPK-based *in silico* frameworks and determine the GI-motility-driven hydrodynamic impacts that should be incorporated into *in vitro* dissolution methods for *in vivo* relevance. Current compendial dissolution methods are not always reliable to predict the *in vivo* behavior, especially not for biopharmaceutics classification system (BCS) class 2/4 compounds suffering from a low aqueous solubility. Developing a predictive dissolution test will be more reliable, cost-effective and less time-consuming as long as the predictive power of the test is sufficiently strong. There is a need to develop a biorelevant, predictive dissolution method that can be applied by pharmaceutical drug companies to facilitate marketing access for generic and novel drug products. In 2014, Prof. Gordon L. Amidon and his team initiated a far-ranging research program designed to integrate (1) *in vivo* studies in humans in order to further improve the understanding of the intraluminal processing of oral dosage forms and dissolved drug along the gastrointestinal (GI) tract, (2) advancement of *in vitro* methodologies that incorporates higher levels of *in vivo* relevance and (3) computational experiments to study the local processes underlying dissolution, transport and absorption within the intestines performed with a new unique CFD based framework. Of particular importance is revealing the physiological variables determining the variability in *in vivo* dissolution and GI absorption from person to person in order to address (potential) *in vivo* BE failures. This paper provides an introduction to this multidisciplinary project, informs the reader about current achievements and outlines future directions.

Introduction

Predicting the *in vivo* biopharmaceutical performance of oral drug products remains challenging, not only because of the properties of the drug but even more because of the drug product itself. In 2014, the University of Michigan was financially supported by the FDA (i) to explore the gastrointestinal (GI) processes that underlie the inter-/intra-subject systemic variability after administration of an oral drug product (task 1) (Hens et al., 2017a; Koenigsknecht et al., 2017; Yu et al., 2017, 2016) (ii) to advance the development of *in vivo*-relevant *in vitro* dissolution testing (task 2) (Kostewicz et al., 2014) and (iii) to develop and apply first-principles mathematical models and a new 'Computational Fluid Dynamics - Particle Model (CFD-PM)' framework to study local processes that underlie absorption within the intestines (tasks 3-4) (Brasseur et al., 2017; Mudie et al., 2015; Wang et al., 2015, 2012). Task 1 of the project initially focused on clinical aspiration/motility studies in healthy volunteers, the main population for *in vivo* bioequivalence (BE) studies. The GI and plasma concentrations of the weakly acidic drug ibuprofen (Biopharmaceutics Classification System (BCS) class IIa) (Amidon et al., 1995; Tsume et al., 2014) were measured after oral administration of an immediate-release (IR) tablet of the reference drug product (Shreveport, LA; Dr. Reddy's - IBU − Ibuprofen Tablets, USP, 800 mg) (Hens et al., 2017a; Koenigsknecht et al., 2017). In parallel, motility pressure events were recorded with water-perfused manometry. The tablet was single-dose administered in fasted state conditions with a glass of water and in fed state conditions with a liquid meal (Pulmocare®, Abbott Nutrition (Lake Forest, IL)) and a glass of water on separate study days. These data served as a reference to develop a formulation predictive (fPD) dissolution apparatus under design to (i) reflect *in vivo* performance of an oral drug product and (ii) explain potential failures in *in vivo* bioequivalence (BE) studies. More future aspiration/motility studies will be performed in order to extrapolate the predictive power of the GIS to different drug compounds (*i.e.,* differences in physicochemical/biopharmaceutical properties). By replacing *in vivo* BE studies by fPD studies, the landscape of oral drug development will be drastically reshaped, both for the development of new as generic drug products. The costs for companies to authorize generic drug products is immense since more than 85% of all patients in the US are treated with generic drug products (Lennernäs et al., 2017a; Lionberger et al., 2013). Cook and Bockbrader calculated that 22-38 million dollars per year per generic

drug product could be saved by making use of the BCS-based biowaivers for BCS class I drugs, assuming that 25% of BE studies are for class I drugs (Cook and Bockbrader, 2002). The same development cost savings can be applied to BCS class III drugs assuming 25% of BE studies are for class III drugs. Besides financial investment costs, *in vitro* studies assess drug product performance more directly compared to conventional pharmacokinetic (PK) studies in which drug absorption is measured indirectly for locally acting drugs (Polli, 2008). This is of particular significance, for example, in the case of oral drug products intended for local therapeutic action in the GI tract, where it is more difficult to connect the therapeutic effect to the plasma concentrations of the drug in the systemic circulation (*e.g.,* sulfasalazine, 5-aminosalicylic acid). Drug product performance can be assessed and evaluated by *in vitro* dissolution and absorption experiments carried out both for the RLD and generic drug product. *In vitro* dissolution methods can also provide more rapid results, without the need of a clinician or willing subjects. This is another reason to replace *in vivo* BE studies by *in vitro* studies; as stated in the 21 CFR 320.25(a) in the USA (U.S. Government Printing Office, 2003), "no unnecessary human testing should be performed". This code states "the basic principle in an *in vivo* bioavailability study is that no unnecessary human research should be done."

To summarize, there is an immense need to develop biorelevant, predictive dissolution methods for application by generic and novel drug companies to facilitate marketing access for a wide-spread variety of oral drug products in terms of formulation type and active pharmaceutical ingredients (APIs) from various BCS classes (Polli et al., 2008, 2004). In 2014, Prof. Gordon Amidon and his team initiated *in vivo* studies in humans to analyze the complexities in the intraluminal behavior of oral dosage forms in the GI tract. Prof. Gregory Amidon lead an effort to develop *in vivo* relevant *in vitro* testing, and Prof. Brasseur lead the development and application of advanced, new mathematical and computer models. Of particular importance is the determination of the physiological variables that underlie intra-/inter-subject variabilities in *in vivo* dissolution and absorption to address (potential) *in vivo* BE failures. This manuscript summarizes the current state of this multidisciplinary project.

General outline of the 21st Century BE project and selected tasks

The strategy of this FDA-funded project is to create an fPD device that can predict the *in vivo* performance of an oral drug product (Task 2). In order to build this robust set of model, *in vivo* data are

required (Task 1). In addition, a new computational fluid dynamics (CFD) high-performance computing framework was developed and applied in two series of computational experiments (Tasks 3-4). To schedule all *in vivo* experiments for this ongoing project, the different objectives are categorized within different tasks:

- **Task 1:** *In vivo* studies: Intraluminal profiling, manometry, magnetic resonance imaging (MRI)

- **Task 2:** *In vitro* studies: Gastrointestinal Simulator (GIS)

- **Task 3 & 4**: *In silico* studies: mass transport modeling (MTM) & computational fluid dynamics – particle model (CFD-PM)

Task 1 is an *in vivo* work package focused on mechanistic *in vivo* biopharmaceutical studies with the focus on intraluminal profiling of drug concentrations in parallel with simultaneously analyzing motility events along the human GI tract. The GI tract is a complex and dynamic organ with large regions, making it a challenge to assess in detail (Grønlund et al., 2017). The first study was an *in vivo* aspiration study that was successfully completed in 37 healthy volunteers (Hens et al., 2017a; Koenigsknecht et al., 2017). A customized multi-channel manometric catheter was intubated by mouth and positioned in the human GI tract of all participating subjects. After oral administration of an 800 mg ibuprofen tablet, GI fluids were aspirated from the stomach, duodenum and jejunum. In parallel, blood samples were taken to measure plasma exposure over time of the study drug. These studies were conducted in fasted (n=20) and fed states (n=17). The results of this study indicated that the *in vivo* drug dissolution is much slower than what is observed using traditional *in vitro* methods, which appears to be primarily due to the low buffer capacity of the intestinal fluids. Moreover, a clear linear correlation was observed between the time when a high burst of phase III contractile waves was present and the maximal concentration of ibuprofen in plasma (plasma C_{max}) (Hens et al., 2017a; Talattof et al., 2016). This study demonstrated the importance of motility and gastric emptying versus pH and buffer capacity as major determinants responsible for the systemic exposure of an orally-administered drug product.

To have an adequate reflection of fluid distribution along the GI tract, a phenol red solution (0.1 mg/mL) was poured into the glass of water that was administered to the subjects in the same study. In this case, we were able to monitor GI fluid changes related to dilution, secretion, and absorption in fasted and fed state conditions. Phenol red is a BCS class 3 compound with negligible absorption characteristics (Dahlgren et al., 2017). Phenol red concentrations were analyzed in the aspirated fluids and will serve as reference data in order to develop an MTM that can reflect the real-life situation of GI fluid changes throughout the entire GI tract (stomach, duodenum and jejunum), respecting the changes in GI physiology in fasted and fed state conditions.

Additional insights into contractile events along the GI tract will be explored by MRI studies in the coming year at the University of Nottingham (Figure 1). MRI is being used to quantify the time courses of the volumes of freely mobile fluid in the stomach and bowel together with GI motility, within the same study session, in healthy adult participants (Khalaf et al., 2015; Mudie et al., 2014; Murray et

al., 2017). In addition to volumes, several MRI studies have already quantified motility by (i) using a registration algorithm that provided a global motility metric in arbitrary units (Menys et al., 2013) or by (ii) administering nonabsorbable fluid to monitor small bowel contractions (Wakamiya et al., 2011). Current work is cross-validating the MRI small bowel motility protocol with the one used previously at the University of Michigan (Hens et al., 2017a). The ultimate aim is to show that invasive manometric intubation methods can be replaced by noninvasive MRI methods. Future plans will include correlating plasma drug time courses with GI fluid volumes and motility in the unprepared and undisturbed (*i.e.,* not intubated) bowel. Although not a main outcome of the primary validation study, the MRI data are also expected to enable identification contractile phases of the migrating motor complex (MMC). The ability of MRI to monitor the entirety of the GI tract and to detect non-occlusive contractions of the lumen should also prove that the MRI methods could actually provide superior information to that obtained under conventional perfused manometry (Wright et al., 1999).
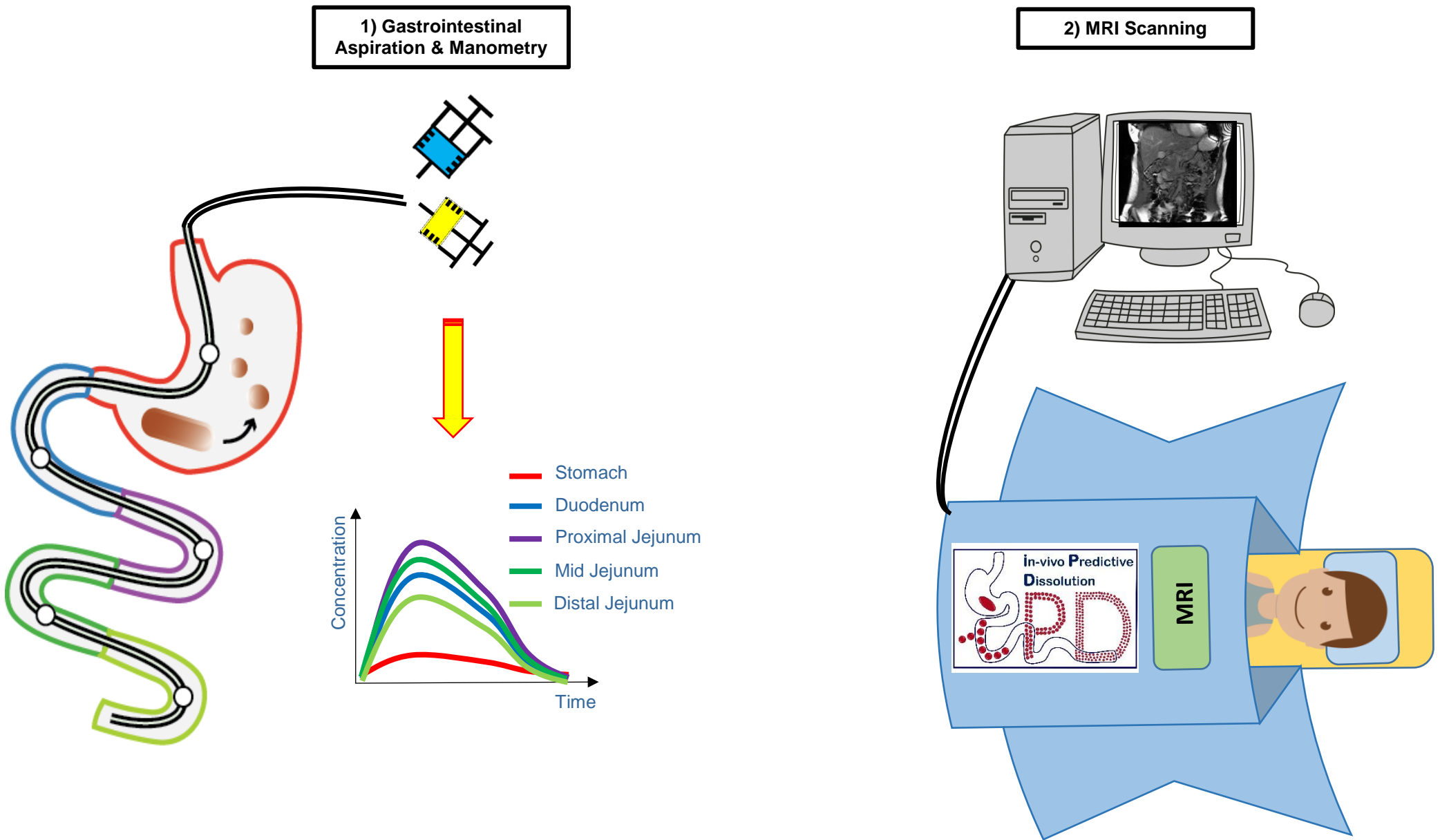
Figure 1: Representative illustration of the 1) aspiration-motility study and 2) MRI scanning study that are performed in task 1 of this BE project.

Task 2 focuses on biorelevant *in vitro* studies that reflect *in vivo* behavior of the oral drug product, as quantified in task 1. There are many in vitro models described in the literature and these tools are subject to optimization/ validation throughout different biopharmaceutical projects at the moment. These models can be classified as rather simple, static models (*e.g.,* USP 2/4 models) towards more complex and dynamic models (*e.g.,* ASD model, BioGIT, Transfer Model and TIMagc) (Carino et al., 2006; Kostewicz et al., 2014; Kourentas et al., 2016; Matsui et al., 2016; Verwei et al., 2016). Under development is the 'Gastrointestinal Simulator' (GIS), consisting of gastric, duodenal and jejunal chambers (Figure 2).
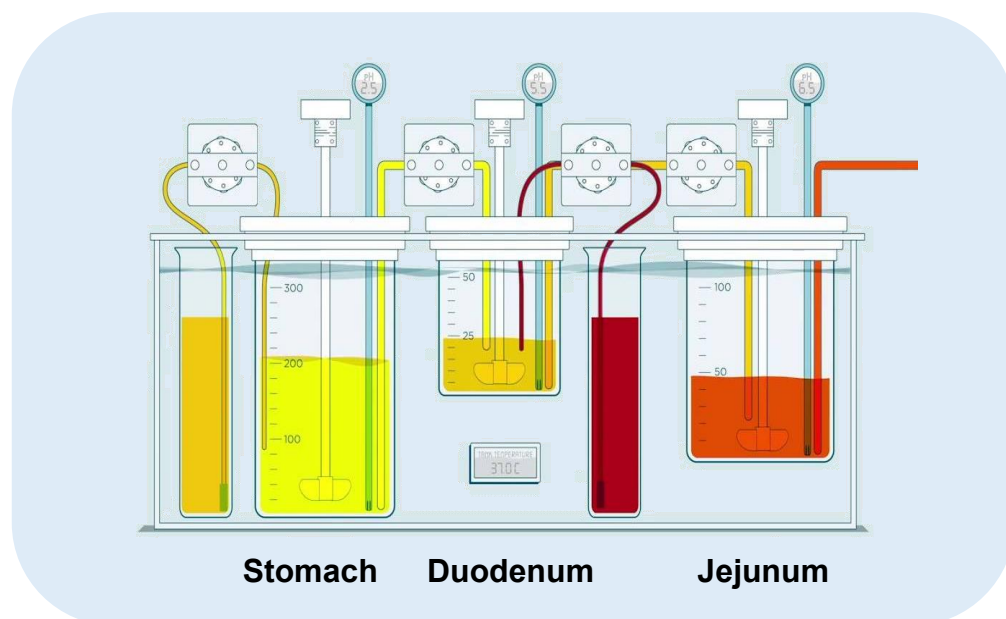

Figure 2: Setup of the GIS consisting of a gastric, duodenal and jejunal chamber. Gastric and duodenal secretions are simulated as well. The pH can be measured during the entire experiment in all compartments. Figure adapted from Hens et al., (2018) - Copyright Elsevier 2018.

The major advantage of this user-friendly model is a directly controlled adjustment of parameters relevant to *in vivo* dissolution and absorption. For example, rapid transfer of gastric emptying has been observed in humans: gastric half-life values from 4 - 13 min in fasted state conditions following a first-order kinetic process (Hens et al., 2014; Tsume et al., 2017). To confirm, Mudie and colleagues demonstrated the same fast, first-order gastric emptying of 240 mL of water in 12 healthy subjects by performing MRI scanning (Mudie et al., 2014). These scenarios can be implemented in the GIS by controlling the rates of the individual peristaltic pumps and the transfer between the gastric and duodenal chambers, duodenal to jejunal chambers, as well as the separate gastric and duodenal secretions. To

simulate absorption, an artificial membrane was recently developed. The creation of an absorptive sink by working with a polydimethylsiloxane (PDMS) membrane to simulate oral drug absorption has recently been investigated and approved (Sinko et al., 2017). The customized PDMS membrane showed biomimetic properties related to the intestinal membrane because of similarities in small molecule transport, such as mechanism, ionization selectivity and lipophilicity. The impact of sink conditions on intraluminal concentrations can be significant as demonstrated by Bevernage and colleagues (Bevernage et al., 2012). In this work, the precipitation kinetics of loviride were evaluated after induction of different supersaturated solutions at the apical side of the Caco-2 setup. The impact of an absorptive environment was evaluated in presence and absence of sink conditions (*i.e.,* by parafilm-sealing the insert and in absence of a cell monolayer). Also, the micellar encapsulation of a lipophilic drug can hamper the intestinal absorption as shown for fenofibrate in man and *in vitro* (Buch et al., 2009; Hens et al., 2015; Sironi et al., 2017). Solubilization of the drug will be enhanced in the presence of colloidal structures such as (mixed) micelles and vesicles, but permeation can be hampered. Only the free fraction (*i.e.,* not encapsulated) will be available for intestinal absorption (Dahan et al., 2016). In that case, respecting the dissolution/permeation interplay is indispensable to make the right predictions towards the *in vivo* performance of the drug. Implementation of the PDMS membrane in the GIS device is currently ongoing and will help us to directly look at formulation performance considering the dissolution/permeation interplay.

The volumes and dissolution media can be adjusted in order to resemble different scenarios consistent with the protocol of the clinical studies. Various studies have been successfully conducted to predict the *in vivo* performance of orally administered BCS class IIb compounds (Matsui et al., 2017, 2016, 2015; Tsume et al., 2015). The obtained *in vitro* dissolution profiles can be applied as an input for a physiologically-based pharmacokinetic (PBPK) model describing absorption, distribution and clearance of the drug of interest. The predicted plasma profiles can be directly compared with observed *in vivo* plasma data. In this way, the GIS device can be evaluated and validated. Moreover, if intraluminal concentration-time profiles of the drug of interest are quantified (*e.g.,* gastric and intestinal determined concentrations), a direct validation of the GIS can be established by directly comparing the *in vitro*

dissolution profiles with the measured intraluminal concentrations. Optimization and validation of the current GIS model will lead, in the end, to a newer version. Currently, attention has been directed at vessel shape and stirrer design to reproduce the mixing conditions as observed *in vivo*. Average shear rates are simulated in different vessel designs to provide an optimal design using different kinds of stirrers in order to select the right vessel and stirrer that closely mimics the *in vivo* shear rates (Baxter et al., 2006, 2005; Kukura et al., 2004). For instance, Figure 3 depicts the CFD in the gastric (A) and duodenal (B) chamber of the GIS device as well as in the (C) USP II dissolution apparatus with a stirring paddle (100 rotations per minute).
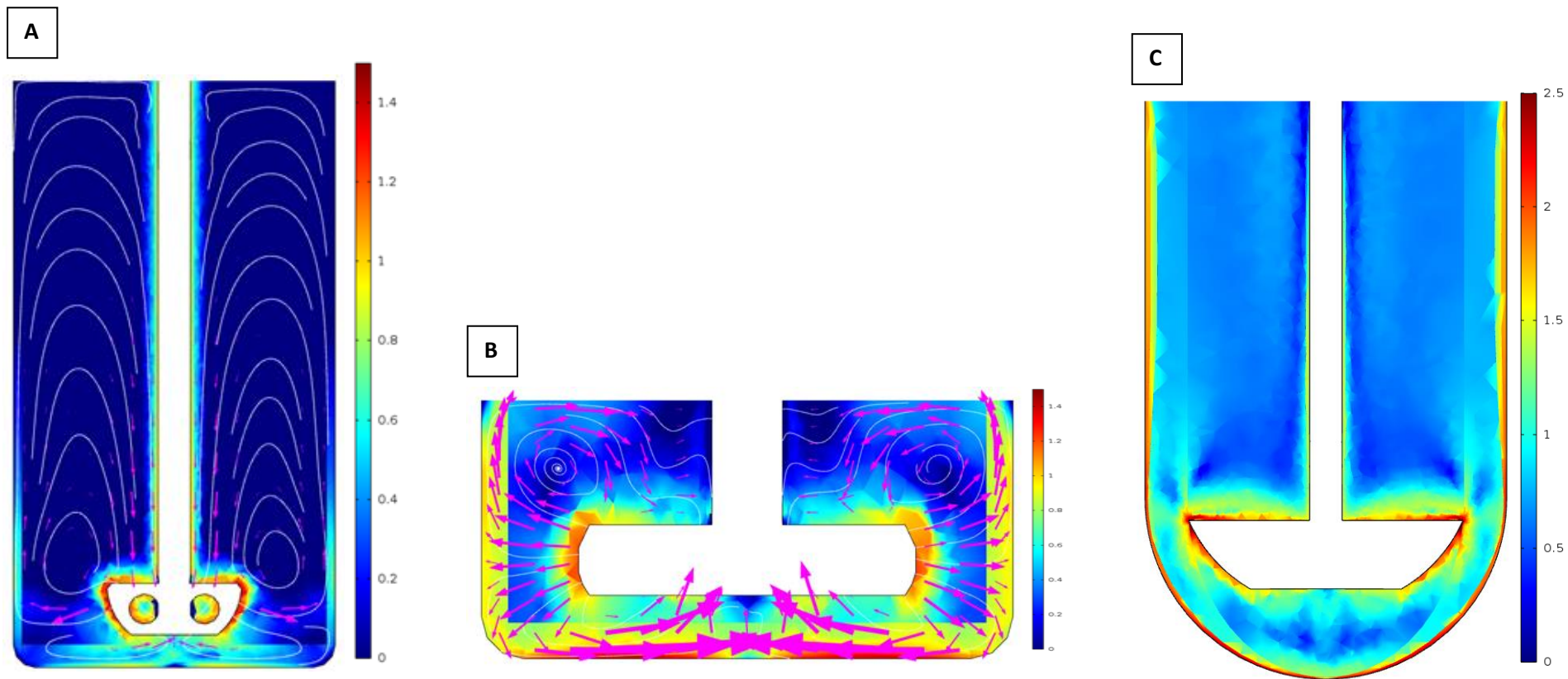
Figure 3: Logarithmic-transformed shear rate values (A) in the stomach compartment of the GIS (25 rotations per minute), (B) in the duodenal compartment of the GIS (25 rotations per minute) and (C) in the USP II dissolution device (100 rotations per minute).USP II dissolution apparatus with stirring paddle (100 rotations per minute). Simulations were performed by applying COMSOL Multiphysics® (Burlington, MA). Partially adopted from Salehi et al., (2017).

Besides hydrodynamics, selection of buffer species (bicarbonate versus phosphate) and buffer concentrations are subject of interest as the low buffer capacity of the aspirated fluids was responsible for the dynamic pH range along the GI tract (Krieg et al., 2015, 2014). Especially for enteric-coated dosage forms, physiological bicarbonate buffers proved to be more discriminative with respect to the drug release behavior. Moreover, the adoption of inappropriate buffer media for *in vitro* BE studies would likely cause a failure in achieving an *in vitro⸺in vivo* correlation (IVIVC) for oral drug products. Therefore, we will investigate the impact of the buffer species on the drug release for different dosage forms during this project.

Task 3 centered on the development and application of mathematical models of the rate of release of drug molecules from individual small spherical drug particles in a 'hierarchical' framework that allows for extensions that can include adjustments to dissolution rate from, among other effects, hydrodynamic (*i.e.,* flow) influences on single-particle dissolution rate. In task 4 we developed a computational fluid dynamics (CFD) framework with an embedded mathematical 'particle model' (PM) that has the 'hierarchical mathematical model' of task 3 at its core (Wang et al., 2015, 2012). The development of the hierarchical mathematical model framework included a major advance in modeling and analysis of hydrodynamic influences on dissolution rate as well detailed analysis of the consequences of variations in solid drug concentration and solubility, particle size distribution and the confinement of drug molecules by vessel boundaries in *in vitro* devices with impermeable containers. This new understanding was embedded within a CFD-PM framework based on the lattice-Boltzmann numerical method (Wang et al., 2010). Using the CFD-PM we have designed and carried two classes of computational experiments on 'high-performance computing' (HPC) platforms, as briefly described below ('HPC' currently implies the application of multi-processor computers requiting parallel processing methods.).

Figure 4 illustrates key issues addressed using the CFD-PM, specifically drug release, transport and absorption within localized fluid-filled 'pockets' of the GI tract. The central point illustrated in this figure is that absorption of drug molecules can take place only if they are presented to the mucosal epithelium, so that absorption depends on the mechanisms underlying the rate at which drug molecules

are transported to the intestinal wall from the bulk fluid in relation to the rate at which drug molecules are released into the bulk. This relationship is driven by the complex array of motility-driven hydrodynamic motions within the stomach and intestines that varies with the physiological and function state of the GI tract. In the fed state, when GI function is directed at nutrient absorption, regular 3/min peristaltic contractions in the gastric antrum coordinate with pyloric opening to allow transport of gastric content into the duodenum at a controlled rate. The dominant motility of the duodenum and jejunum in the fed state is peristalsis, both forward and reversed for transport and mixing, and segmental contractions that enhance mixing locally (Ailiani et al., 2009; Banco, 2010). The fasting state is characterized by lack of nutrients in the GI tract, and therefore lack of function associated with nutrient absorption. Motility in the fasting state is characterized by the MMC which occurs in roughly three phases that repeat with a period typically in the range of 60-90 minutes. Whereas phase I is characterized by overall quiescence, phases II and III involve motility patterns that can be disorganized or organized and which involve peristalsis locally at very different spatial and temporal scales. We have begun to study these relationships in the jejunum using the new CFD-PM developed under the current FDA program.
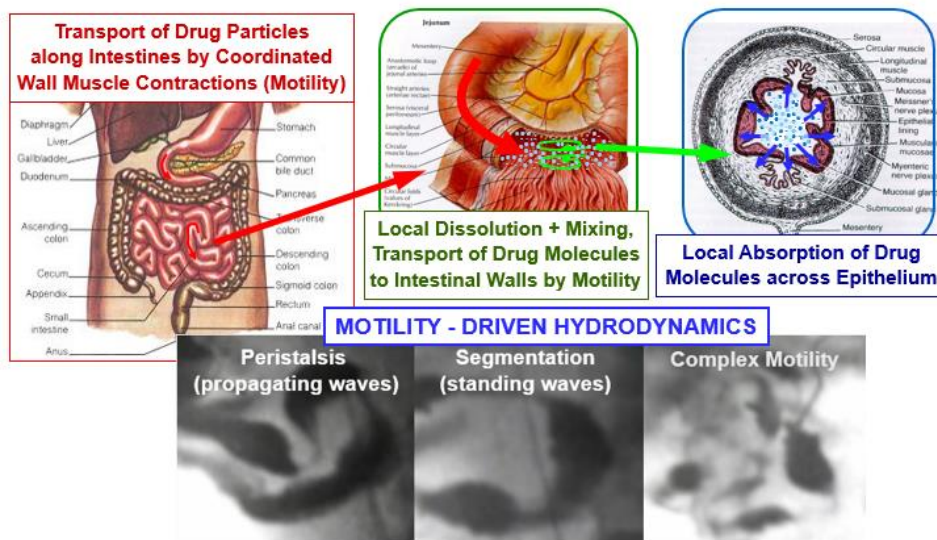
Figure 4: The role of intestinal transport and contractile patterns (motility) on motility in drug release (dissolution), drug particle and molecular transport, and drug absorption. The upper images illustrate global transport of intestinal content (upper left image) by peristaltic contractile patterns (left lower image). Peristalsis both transports and mixes drug particles (middle upper image) as drug molecules are released and mixed and absorbed (upper right image) within localized "pockets" of fluid that change in time by the axially moving local contractile patterns (lower left image). In addition, standing wave "segmentation" motility patterning (lower middle image) predominantly mix drug particles and molecule locally within pockets, and increases lateral transport of drug molecules to the mucosal surface (upper right image), where they can be absorbed. Whereas peristalsis and segmentation are the more common canonical motility patterns, more complex patterns, with mixes of peristalsis and segmentation, can occur (bottom right image), as are periods with little or no motility. Each different motility pattern impacts hydrodynamic contributions to dissolution and transport differently.

The CFD-PM framework is designed to predict the development and spatio-temporal evolution of the local concentration field in response to the release of drug molecules from the surfaces of thousands of drug particles of varying diameter. Both the particles and the drug molecules are carried by the local velocity field resulting from spatio-temporal contractions of the intestinal (or gastric) lumen. To date, two sets of computational experiments for release, transport and absorption of ibuprofen (a class II weak acid with pKa ~ 4.4) have been performed. All experiments carried out to date have applied a geometry model for peristaltic motility using data from Mudie et al., (2014) to estimate 'small' and 'large' intestinal pocket volumes within the true fasting state *in vivo* range of 2.0 and 12.1 mL, respectively (Figure 5).
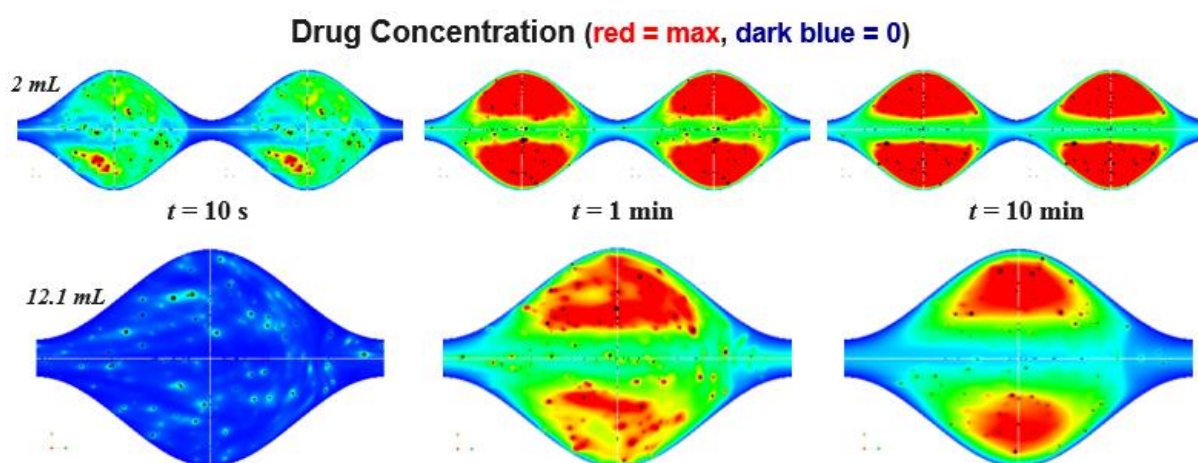
Figure 5: Drug concentration at cross section of the intestinal pockets for large and small volumes and with the maximum permeability boundary condition at different times during the transition from an initial state when no drug has been released into the bulk fluid to a quasi-steady state period when the structure of the concentration field remains roughly constant in time. Maximum concentration is shown in dark red and zero concentration in dark blue in a frame-of-reference moving with the peristaltic waves. The quasi-steady period starts earlier with smaller pocket volumes and lasts for 50-60 minutes before a long-lasting final period over which all particles have dissolved and all released drug molecules have been absorbed (end simulation run: 180 min). Both drug concentration and particle concentration (not shown) develop a highly heterogeneous distribution as a result of the motility-forced velocity field. In this "max permeability" scenario, absorption results from a balance between transport (advection) into a central "bubble" of recirculating flow and diffusion of drug molecules from the recirculating bubble across a narrow fluid layer to the mucosal surface.

In Figure 5 we show the center plane of trains of peristaltic waves at different times during the initial period in drug release from 4216 particles over a range of particle sizes measured from the IR ibuprofen tablet (Shreveport, LA; Dr. Reddy's - IBU − Ibuprofen Tablets, USP, 800 mg). From one of the very few studies with *in vivo* data from which peristaltic wave speeds in the fasting state can be

estimated (Castedal and Abrahamsson, 2001), we estimated peristaltic wave speed for peristaltic events in the phase III MMC period to be of order 1 cm/s. During this period a highly heterogeneous distribution of drug concentration develops, largely driven by the details of the pocket velocity field driven by peristalsis. Drug absorption, which takes place at the surface, results from an interaction between bulk transport of particles and concentration by the velocity within the 'trapped' fluid regions, shown in Figure 5 by the region with the highest drug concentration (red area), and diffusion of drug molecules from this trapped region to the mucosal surface. We find that a quasi-steady state period is established within roughly 1 min for the 2 mL pocket and within roughly 10 min for the 12.1 mL peristaltic pockets. We also find that hydrodynamic enhancement of dissolution and absorption rate from slip velocity (convection) is only a 1-2% effect while the shear-rate effect is very strong, causing a 40-50% increase in dissolution and absorption rate compared to pure diffusion. A number of important mechanistic processes and their interactions uncovered and analyzed will be discussed in forthcoming scientific papers.

Concluding remarks & Future Perspectives

The intensive collaborations among gastroenterologists, statisticians, chemical engineers, pharmaceutical scientists and regulatory authorities are indispensable in this project in order to achieve our goals (Table 1).

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Table 1: Overview of all participating parties in this 21st Century BE project.

Similar efforts are ongoing in European projects, such as OrBiTo (http://www.orbitoproject.eu) (Lennernäs et al., 2014). This project is funded by the Innovative Medicines Initiative (IMI) and the European Federation of Pharmaceutical Industries and Associations (EFPIA). The same philosophy/vision is centralized in this project: "Transform our ability to predict the *in vivo* performance of oral drug products across all stages of drug development". This six-year ongoing project (2012-2018) demonstrated the closed interaction and collaboration between academic institutions and pharmaceutical companies in order to increase the predictive power of biorelevant *in vitro/in silico* models that are frequently used in preclinical formulation development (industry-driven project).

In 2016, The PEARRL project kicked off and received funding under the Marie Skłodowska-Curie Innovative Training Networks of the Horizon 2020 program of the European Union. The members of this project consist of 9 beneficiaries and 10 partner organizations from 8 different countries, closely collaborating on biopharmaceutical themes with a regulatory link. All partners employ 15 PhD researchers that will be trained/prepared to mature scientists after an intensive training of three years in an academic, industrial and regulatory setting (http://www.pearrl.eu).

More recently, a new action (The European Network on Understanding Gastrointestinal Absorption-related Processes (UNGAP)) got set up to manage a multidisciplinary network of scientists aiming to advance the field of intestinal drug absorption by concentrating on four major challenges: (i) differences between specific patient populations, (ii) regional differences along the GI tract, (iii) the intraluminal behavior of advanced formulations, and (iv) food-drug interactions. This European cooperation in science and technology (COST) action seeks to connect specialists in different pharmaceutical/medical fields in order to unravel the black boxes of the GI tract. This action is financially supported by the Horizon 2020 Framework program of the European Union (http://www.ungap.eu).

Regarding all these ongoing projects worldwide, a broad discussion is recently started for an International Conference on Harmonization (ICH) initiative on BE. It is an ongoing process to define regional global differences on IVIVC and BE (Lennernäs et al., 2017b). For instance, the ingested volume of water co-administered in clinical studies with the oral drug product differ between continents (240 mL for FDA and EMA versus 150 mL for PDMA) (European Medicines Agency, 2010; Food & Drug Administration, 2015; Pharmaceuticals and Medical Devices Agency, 2012). Recent studies in Japan and Belgium showed that barely anyone takes their oral medicines with a full glass of water, but rather with 88 mL (Japan; n=512) or 125 mL (Belgium; n=1977) (Hens et al., 2017b; Sugihara et al., 2015).

The human studies as described in task 1 will result in a comprehensive human database in terms of measured drug concentrations along the GI tract and measured impact of the dynamic physiology on these concentrations. For the next years, the focus will encompass MRI studies that will investigate and quantify dynamic and physiological aspects of the GI tract: fluid volumes, motility and transit. In a second step, the MRI study will be extended to oral administration of a drug product and blood sampling under MRI monitoring of the bowel. This approach opens horizons to look at oral drug product processing in any kind of population: pregnant/childbearing/lactating women, specific patient populations, children and elderly. To conclude, because of this multidisciplinary approach, we will extend our fundamental knowledge of the GI tract to deliver a formulation predictive dissolution apparatus that will support generic and new drug product development.

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