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Resolving intraluminal drug and formulation behavior: Gastrointestinal concentration profiling in humans

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ABSTRACT

Despite the wide use of the oral route to deliver systemic drugs to humans, the intestinal absorption process is still not fully understood. Especially for complex absorption-enabling strategies (e.g. solubilization, supersaturation, etc.), the in vivo performance is difficult to predict. Considering the current share of drug candidates that suffer from a non-favorable absorption potential and therefore rely on these strategies, there is a growing interest in approaches that aim to resolve the multitude of interactions between drugs, formulation factors and the gastrointestinal environment. In this respect, gastrointestinal concentration profiling following drug administration to humans is a recent but promising strategy that complements more established techniques including gastrointestinal imaging. In the present review, a number of case studies will be discussed to demonstrate the added value of gastrointestinal concentration profiling to gain in-depth knowledge of intraluminal drug and formulation behavior and to identify those processes key for drug absorption. Examples include a better understanding of intestinal precipitation of weakly basic drugs, clarifying inter-individual or food-induced variability in absorption, and an improved insight into the solubility-permeability interplay. As manifested in a recently initiated European project on oral biopharmaceutics tools (OrBiTo), intraluminal concentration profiling will contribute to the development of relevant simulation models that are built upon a solid understanding of human drug and formulation behavior, and allow for a more predictive in vitro and in silico evaluation of absorption.

1. Introduction

Impaired intestinal absorption, causing insufficient or variable bioavailability, is one of the key reasons for suboptimal clinical performance of orally administered drugs with systemic action. Reliable preclinical prediction of absorption during drug candidate selection and formulation development is of paramount importance to tackle absorption issues and reduce drug attrition during clinical trials. Classically, in vitro evaluation of absorption involves assessment of the drug's absorption potential (i.e. solubility and permeability) and, in the course of formulation development, dissolution in static, one compartment setups (USP apparatus I and II). While these approaches may suffice to forecast uptake of easily absorbed molecules, they are less accurate as in vivo predictive tools for molecules with less favorable absorption potential (i.e. limited solubility and/or permeability). Enabling absorption of these compounds requires sometimes challenging formulation strategies of which the performance greatly depends on the gastrointestinal physiology and the interplay between multiple processes, as schematically represented in Fig. 1. Attempts to capture this interplay in biorelevant in vitro evaluation tools have resulted in the development of dynamic, multicompartmental systems to account for time-dependent fluid composition, gastrointestinal transit and/or permeation (e.g. USP apparatus IV, dissolution-permeation system, TNO Intestinal Model) (McAllister, 2010). In addition, computational physiologically based models have been anticipated as powerful tools to integrate in vitro data and simulate the human absorption process (physiology-based (PBPK) pharmacokinetic modeling) (Kostewicz et al., 2013a). For many drug-formulation combinations, however, the predictive power of these models still appears either insufficient or uncertain (Kostewicz et al., 2013b).

Further model optimization is often impeded by gaps in the knowledge on the in vivo behavior of complex formulations in the gastrointestinal tract. An example that currently receives much attention is the precipitation of drugs in the stomach or intestine. Since the induction of intraluminal supersaturation has recently

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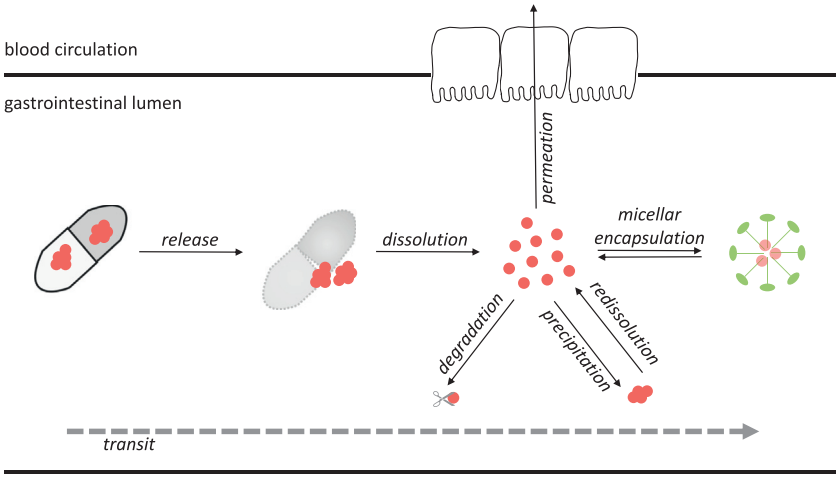

Fig. 1. Schematic and simplified representation of intraluminal processes determining intestinal absorption.

become a promising and widely investigated formulation strategy to enable absorption of poorly soluble drugs, assessment of possible precipitation prior to drug uptake is crucial to evaluate the potential of supersaturating drug delivery systems. However, the knowledge on in vivo precipitation in the gastrointestinal tract is nearly non-existing and recent studies suggest that most in vitro simulations of precipitation are inaccurate (Bevernage et al., 2013). To overcome these types of obstacles, reference studies that assess the intraluminal fate of drugs and dosage forms in humans are receiving intensified attention. This has recently been manifested within the Oral Biopharmaceutics Tools (OrBiTo) project. OrBiTo, a new project within the Innovative Medicines Initiative (IMI) between the European Union and the European Pharmaceutical Industry Association (EFPIA), pursues the development of novel, in vivo predictive experimental and theoretical models for oral absorption (Lennernäs et al., 2013). One of the main pillars of OrBiTo is a thorough understanding of the absorption process that should support these novel tools.

In this framework, the present review aims to demonstrate the assessment of gastrointestinal concentrations upon oral drug administration as a recent tool to evaluate intraluminal drug and formulation behavior in humans and to guide the optimization of simulation models.

2. Evaluating gastrointestinal drug and formulation behavior in humans

Traditionally, the development of in vitro models that aim to simulate intestinal drug absorption is driven by reference data from classic pharmacokinetic studies. This implies, at best, indirect assessment of the underlying intraluminal processes through modeling of systemic concentration–time profiles using, for instance, deconvolution or PBPK modeling. It has been recognized that only direct evaluation of the intraluminal behavior allows for an in-depth understanding of the complex interplay between gastrointestinal physiology and drug formulations. For this purpose, both imaging and intubation techniques can be used.

2.1. Imaging techniques

Imaging of the gastrointestinal tract allows for a non-invasive way to follow the fate of orally administered dosage forms without disturbing physiological processes. The historical gold standard is gamma scintigraphy, but more recently, alternative approaches have been introduced based on magnetic tracking principles. In this paper, the different techniques, including their strengths and weaknesses, are only shortly raised; for a detailed discussion, we refer to recent reviews on this topic (Corá et al., 2011; Weitschies and Wilson, 2011; Weitschies et al., 2010).

Gamma scintigraphy has been applied to investigate the gastrointestinal behavior of pharmaceutical dosage forms since 1976 (Casey et al., 1976; Wilding et al., 2001). In this method, a dosage form is labeled with a gamma-emitting radioisotope, either by direct incorporation during formulation (^{99m}Tc or ^{111}In) or by neutron activation of a stable isotope (e.g. ^{152}Sm, activated to ^{153}Sm). Subsequently, the distribution of these isotopes in the gastrointestinal tract can be assessed by means of a scintillation camera, which generates a two-dimensional projected view. This allows monitoring the intraluminal location of the labeled dosage form (transit) and its integrity (release) over the entire length of the gastrointestinal tract. The approach has been used to evaluate the residence time in the stomach, small intestine and colon in different conditions (e.g. fasted versus fed state). Furthermore, the combination of scintigraphy with pharmacokinetic studies (pharmacoscintigraphy) has become an important means of increasing insight into the impact of transit and release of oral dosage forms on drug absorption.

The main disadvantage of scintigraphy is the necessity to apply ionizing radiation, requiring essential precautions and regulatory issues. Alternative imaging techniques that avoid this type of strain to volunteers and investigators are based on the detection of magnetically labeled dosage forms (Corá et al., 2011), including the method of magnetic marker monitoring (MMM) (Weitschies et al., 2010). For MMM, the dosage form is marked as a permanent magnetic dipole by the incorporation of ferromagnetic material and subsequent magnetization in a strong magnetic field. After oral administration, the three dimensional localization of the dosage form (i.e. the magnetic source) in the gastrointestinal tract can be monitored as a function of time. Compared to scintigraphy, the high temporal (real-time) and spatial (1 mm) resolution of MMM allows for a more detailed insight into gastrointestinal transit. In addition, disintegration of the dosage form can be quantitatively monitored, as it is related to a decrease in magnetic strength. Once released, however, particles cannot be visualized anymore.

2.2. Intubation techniques

Catheters introduced through the nose, mouth or rectum allow for direct access to the contents of the gastrointestinal tract of human volunteers. Apart from aspirating gastric and intestinal fluids