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Evaluation and optimized selection of supersaturating drug delivery systems of posaconazole (BCS class 2b) in the gastrointestinal simulator (GIS): An *in vitro-in silico-in vivo* approach

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ABSTRACT

Supersaturating drug delivery systems (SDDS) have been put forward in the recent decades in order to circumvent the issue of low aqueous solubility. Prior to the start of clinical trials, these enabling formulations should be adequately explored in *in vitro/in silico* studies in order to understand their *in vivo* performance and to select the most appropriate and effective formulation in terms of oral bioavailability and therapeutic outcome. The purpose of this work was to evaluate the *in vivo* performance of four different oral formulations of posaconazole (categorized as a biopharmaceutics classification system (BCS) class 2b compound) based on the *in vitro* concentrations in the gastrointestinal simulator (GIS), coupled with an *in silico* pharmacokinetic model to predict their systemic profiles. Recently published intraluminal and systemic concentrations of posaconazole for these formulations served as a reference to validate the *in vitro* and *in silico* results. Additionally, the morphology of the formed precipitate of posaconazole was visualized and characterized by optical microscopy studies and thermal analysis. This multidisciplinary work demonstrates an *in vitro-in silico-in vivo* approach that provides a scientific basis for screening SDDS by a user-friendly formulation predictive dissolution (fPD) device in order to rank these formulations towards their *in vivo* performance.

1. Introduction

It is estimated that 90% of the drug molecules in the discovery pipelines suffer from poor aqueous solubility (Loftsson and Brewster, 2010). Whether a poorly soluble molecule can become a therapeutic oral drug product is dependent on the ability to come up with a bioavailability-enhancing approach. 'Resolving' the issue of low aqueous solubility can be established by looking for an enabling formulation that will enhance drug dissolution in such way that supersaturated concentrations can be achieved, increasing the fraction of dissolved drug available for intestinal absorption (Brouwers et al., 2009; Williams et al., 2013). Besides enabling formulations, supersaturation in the small intestine can also be created for basic drugs based on the pH-shift from the stomach (*i.e.*, high solubilizing environment) to the small intestine (*i.e.*, low solubilizing environment) (Kostewicz et al., 2004). The concept of supersaturation as an effective oral bioavailability-enhancing approach has gained a lot of attention over the last decades. When consulting the ISI Web of Knowledge® database, mapping to the topics 'Supersaturation AND Precipitation AND Oral Absorption', the number of publications has been gaining momentum over the last decade as depicted in Fig. 1.

These enabling formulations that are responsible for creating supersaturated concentrations along the gastrointestinal (GI) tract are so-called supersaturating drug delivery systems (SDDS) (Brewster et al., 2008; Gao and Shi, 2012; Laitinen et al., 2017). Throughout the years, a lot of *in vitro* research studies have been conducted in order to understand how these SDDS would actually behave in the human GI tract and exhibit their plasma profile after oral administration. A systematic and

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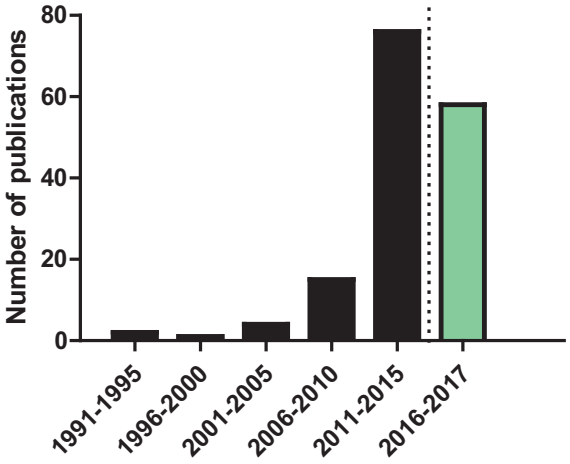

Fig. 1. Number of publications per five years in the ISI Web of Knowledge® database mapping to the topics 'Supersaturation' AND 'Precipitation' AND 'Oral Absorption' (last accessed on 10/02/2017). The green bar presents the number of publications gathered from 2016 until now. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

quantitative synopsis of the knowledge about SDDS has recently been published by Fong and colleagues (Fong et al., 2016). As an extensively and publicly debated topic, there are some important aspects that should be considered in order to gain valuable information about the biorelevant supersaturated concentrations and precipitated amounts of the administered drug (Bevernage et al., 2013; Lu et al., 2017; Sun et al., 2016; Sun and Lee, 2013). There are multiple *in vitro* models described in the literature that are frequently applied to evaluate supersaturation and precipitation for oral drug products; some of these models are more simple and static while other models are more complex and dynamic (Kostewicz et al., 2014b). Since supersaturation is a metastable state and the driving force for precipitation, an appropriate *in vitro* methodology to evaluate these phenomena is, needless to say, paramountly important for the efficient development and optimization of SDDS. For the last five years, several clinical aspiration studies have been performed in order to shed light on the *in vivo* performance of SDDS (Brouwers et al., 2017; Rubbens et al., 2016; Stappaerts et al., 2015). Using these data as a reference, multiple *in vitro* dissolution methodologies have been evaluated and optimized in order to improve their predictive power (Kourentas et al., 2016; Polster et al., 2010; Verwei et al., 2016). The gastrointestinal simulator (GIS) is one of these models that was successfully evaluated for forecasting the *in vivo* performance of different weakly basic compounds (BCS class 2b drugs) that were tested in human aspiration studies (Matsui et al., 2015, 2016; Tsume et al., 2014, 2017a). The reason for its success is likely due to the biorelevance of how this model was built: GI variables (*e.g.*, pH, gastric emptying, secretions, transit times) are integrated into a physiologically-relevant manner in order to mimic and capture the *in vivo* performance of the oral drug product as good as possible.

Especially for enabling formulations (*e.g.*, amorphous solid dispersions), GI variables such as gastric emptying and residual GI volumes are known to have a major impact on drug's behavior along the GI tract and thus are indispensable elements to be integrated into a formulation predictive dissolution (fPD) test (Hasler, 2008; Hens et al., 2016c; Mudie et al., 2014; Murray et al., 2017). Moreover, for delayed or controlled release drug products, a simple dissolution test may not be fully able to capture the *in vivo* performance of these oral drug products. Formulation scientists would require more comprehensive information coming from a more dynamic, multi-compartmental *in vitro* device rather than a simple dissolution methodology. The generated *in vitro* dissolution profiles can be used as an input for *in silico* models in order to produce predicted plasma profiles which can directly be compared with the *in vivo* plasma profiles (Kostewicz et al., 2014a). This 'biopredictive dissolution' approach has emerged as a preferred option whenever pharmacokinetic data are available in order to validate the predictiveness of the *in vitro* model.

To this end, the purpose of this work was to evaluate the *in vivo* performance of four different oral formulations of posaconazole by performing dissolution studies in the GIS. The generated dissolution profiles served as an input for a computational pharmacokinetic model in order to simulate the systemic profiles of posaconazole. Intraluminal and systemic concentrations of posaconazole for the different formulations served as a reference to compare between *in vitro* and *in vivo* data, as recently published by Hens et al. (Hens et al., 2016a, 2016b). In addition, the morphology of formed precipitate of posaconazole was visualized and characterized by optical microscopy studies by optical microscopy studies and thermal analysis. This work demonstrates an *in vitro-in silico-in vivo* approach that gives us a rational framework and scientific basis for screening different oral drug products of the same drug compound by a user-friendly fPD device in order to select the most effective formulation for clinical studies in terms of oral bioavailability.

2. Materials and methods

2.1. Chemicals

Posaconazole and hydroxypropylmethylcellulose acetate succinate (HPMC-AS) was kindly donated by the Chemical Research Division of MSD (MSD Research laboratories, Merck Sharp & Dohme Corp., Kenilworth, NJ, USA). Acetonitrile was obtained from VWR International (West Chester, PA). Methanol, HCl and trifluoroacetic acid (TFA) were purchased from Fisher Scientific (Pittsburgh, PA). NaOH, NaCl and $NaH_2PO_4{\cdot}H_20$ were received from Sigma-Aldrich (St. Louis, MO). Purified water (filtrated and deionized) was used for the analysis methods and dissolution studies to prepare the dissolution media (Millipore, Billerica, MA).

2.2. Design of the in vitro dissolution studies performed with the GIS

The GIS is a three-compartmental dissolution device, which consists of (i) a gastric chamber ($GIS_{Stomach}$), (ii) a duodenal chamber ($GIS_{Duodenum}$) and (iii) a jejunal chamber ($GIS_{Jejunum}$). The design of the GIS is depicted in Fig. 2 (Tsume et al., 2017b).

Four different formulations were tested in the GIS:

1. a solution of posaconazole (pH 1.6; 20 mg dissolved in 240 mL of tap water);
2. an acidified suspension of posaconazole (pH 1.6; 40 mg dispersed in 240 mL of tap water);
3. a neutral suspension of posaconazole (pH 7.1; 40 mg dispersed in 240 mL of tap water);
4. a solid dispersion tablet of posaconazole (100 mg with 240 mL of tap water).

The manufacturing of both suspensions and solution were conducted by dispersing/dissolving Noxafil® suspension (Merck Sharp & Dohme Corp., Kenilworth, NJ, USA) in 240 mL of tap water. The solid dispersion tablet (Merck Sharp & Dohme Corp., Kenilworth, NJ, USA) was used as such without any manipulation. The formulations were poured into/added to the stomach compartment at the start of the study. The dissolution media, initial volumes and secretion rates are described in Table 1.

Gastric emptying occurred by a first-order kinetic process with a gastric half-life of 13 min, in line with the gastric half-life as measured in humans for liquids, ranging from 4 to 13 min (Hens et al., 2014). Duodenal volumes were kept constant during the entire experiment at a volume of 50 mL. The jejunal compartment was left empty initially (*i.e.*, no volume present). As soon as the experiment started, volumes of the $GIS_{Stomach}$ were transferred to the $GIS_{Duodenum}$ *via* a transfer tube by a