Analysis of the impact of controlled release formulations on oral drug absorption, gut wall metabolism and relative bioavailability of CYP3A substrates using a physiologically-based pharmacokinetic model

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ABSTRACT

Controlled release (CR) formulations are usually designed to achieve similar exposure (AUC) levels as the marketed immediate release (IR) formulation. However, the AUC is often lower following CR compared to IR formulations. There are a few exceptions when the CR formulations have shown higher AUC. This study investigated the impact of CR formulations on oral drug absorption and CYP3A4-mediated gut wall metabolism. A review of the current literature on relative bioavailability (Frel) between CR and IR formulations of CYP3A substrates was conducted. This was followed by a systematic analysis to assess the impact of the release characteristics and the drug-specific factors (including metabolism and permeability) on oral bioavailability employing a physiologically-based pharmacokinetic (PBPK) modelling and simulation approach. From the literature review, only three CYP3A4 substrates showed higher Frel when formulated as CR. Several scenarios were investigated using the PBPK approach; in most of them, the oral absorption of CR formulations was lower as compared to the IR formulations. However, for highly permeable compounds that were CYP3A4 substrates the reduction in absorption was compensated by an increase in the fraction that escapes from first pass metabolism in the gut wall (Fg), where the magnitude was dependent on CYP3A4 affinity. The systematic simulations of various interplays between different parameters demonstrated that BCS class 1 highly-cleared CYP3A4 substrates can display up to 220% higher relative bioavailability when formulated as CR compared to IR, in agreement with the observed data collected from the literature. The results and methodology of this study can be employed during the formulation development process in order to optimize drug absorption, especially for CYP3A4 substrates.

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1. Introduction

The magnitude of oral drug absorption and systemic availability are consequences of the interplay between parameters related to the drug itself, drug product (formulation), study condition and the system, i.e., the human body. Hence, drug-specific physicochemical and biopharmaceutical characteristics, together with anatomical and physiological factors, will determine a drug’s oral bioavailability (F) in a given scenario. F is the product of the fraction of the drug that is absorbed (fA) and the fractions that escape from pre-systemic metabolism in both the gut wall (Fg) and the liver (Fl) (Lin et al., 1999).

Formulation characteristics can play a critical role in the drug absorption process. This applies in particular for drugs for which dissolution, solubility and/or permeability characteristics represent the limiting steps for oral absorption, namely, drugs that do not belong to class 1 in the Biopharmaceutics Classification System (BCS) (Amidon et al., 1995; Wilding, 1999). The BCS defines four classes based on a compound’s aqueous solubility and intestinal permeability (high solubility and high permeability (class 1), low solubility and high permeability (class 2), high solubility and low permeability (class 3), low solubility and low permeability (class 4)) (Amidon et al., 1995). In general, the selection of a specific formulation is based on its minimal negative impact on the drug absorption rate, i.e., immediate release (IR) formulations. However,
there are circumstances for which controlling the release rate of the drug from the formulation into the gastrointestinal (GI) lumen is desirable (Langer, 1990). Hence, understanding the potential kinetics of oral absorption for the so-called controlled release (CR) dosage forms and the prediction of their behaviour based on in vitro information is valuable.

CR formulations provide certain advantages when compared to their IR counterparts. CR formulations can reduce peak to trough fluctuations in the plasma concentration–time profile (compared to multiple-dose administration of an IR product), hence reducing fluctuation-related side effects and/or sub-therapeutic concentrations. CR formulations can increase the exposure over time of drugs with a short elimination half-life, and can be used to target delivery into distal regions of the intestine (e.g. colon), or where there is a need for targeted delivery for the treatment of a specific disease, such as Crohn’s disease (Langer, 1990; Rubinstein, 2005; Thombre, 2005). This can lead to an increased patient compliance. Furthermore, CR formulations can be of use in drug development when the standard IR formulation is not an alternative due to unfavourable pharmacokinetic properties of the drug candidate (Langer, 1990; Rubinstein, 2005; Thombre, 2005).

One of the main goals when developing a CR formulation of a marketed drug is to achieve, at least, the same exposure as the equivalent dose of their IR counterpart. In general however the relative bioavailability of a CR formulation compared to its IR counterpart is expected to be less than 100% (European Medicines Agency, 2013). Several physiological factors can influence the observed differences in systemic exposure between IR and CR. A CR formulation is intended to release its drug content within 12–24 h, in contrast the small intestinal transit time is around 2–5 h (Davis et al., 1986; Fallingborg et al., 1989; Yu et al., 1996). Therefore a majority of the dose should be released into distal regions of the small intestine and the colon, where the residence time in the colon is about 12–24 h (Coupe et al., 1992; Davis et al., 1986; Fallingborg et al., 1989). The extended release may limit the absorption potential for a drug formulated as CR as, in general, the distal regions of the intestine provide a less favourable environment for drug absorption. For instance, the reduced surface area available for absorption in the distal region of the GI tract may limit the absorption for poorly permeable compounds (Tannergren et al., 2009; Watts and Llum, 1997), the intestinal pH increases towards the distal portion of the intestine consequently limiting the aqueous solubility of basic compounds (Fallingborg et al., 1989). Finally, the lack of bile salts, less fluid volume in the colon, differences in the regional permeability and possible degradation by colonic microflora can also have a negative impact on the drug absorption of CR formulations (Lennernas, 2014a; Schiller et al., 2005; Sutton, 2009; Tannergren et al., 2009).

Regardless of the unfavourable conditions for the absorption in the distal regions of the GI tract, there are a few examples in the literature were CR formulations of a marketed drug can display higher relative bioavailability compared to their IR formulations. For instance, a single-dose study of a CR formulation of buspirone (5-hydroxytryptamine 1A (5-HT) partial agonist) showed a relative bioavailability of 170–190% as compared to a similar dose of an IR formulation (Sakr and Andheria, 2001b) producing an almost 3.3-fold higher exposure at steady-state (Sakr and Andheria, 2001a). For oxybutynin (anticholinergic), the CR formulation displayed a relative bioavailability of 153% as compared to the IR formulation (Gupta and Sathyam, 1999). Additional studies have showed that the CR formulation of oxybutynin significantly reduced the anticholinergic side-effects of oxybutynin as compared to the IR formulation, without reducing the efficacy of oxybutynin for the treatment of urinary incontinency (Comer and Goa, 2000; Gupta et al., 1999; Sathyam et al., 2001).

Despite almost complete absorption, both buspirone and oxybutynin display an oral bioavailability of around 4% and 6%, respectively, due to extensive first-pass metabolism in the gut wall and liver (Douchamps et al., 1988; Gammans et al., 1985; Lukkari et al., 1998; Mizushima et al., 2007; Yaich et al., 1998; Zhu et al., 2005). Cytochrome P450 (CYP) 3A4 is believed to be the main enzyme responsible for the metabolism of oxybutynin and buspirone (Douchamps et al., 1988; Gammans et al., 1985; Lukkari et al., 1998; Mizushima et al., 2007; Yaich et al., 1998; Zhu et al., 2005). Therefore it has been hypothesized that the observed differences between CR and IR formulations are a consequence of the distribution pattern of CYP3A along the small intestine (Gupta and Sathyam, 1999; Sakr and Andheria, 2001a, 2001b; Tubic-Grozdanis et al., 2008). The abundance of CYP3A varies along the membrane of the small intestine, being higher in the upper region and decreasing towards the distal region and colon (Berggren et al., 2007; Paine et al., 1997; Zhang et al., 1999). Therefore, the CR formulation of such drugs would release most of its drug content into intestinal regions with a lower abundance of CYP3A, thus potentially bypassing the CYP3A-mediated first pass metabolism. This hypothesis is supported by an observed reduction in the exposure of the metabolites of both buspirone and oxybutynin when administered as a CR formulation vs. their IR formulations (Gupta and Sathyam, 1999; Sakr and Andheria, 2001a, 2001b). The reduction in exposure of oxybutynin’s metabolite, N-desethoxybutynin, could also explain the reported improvements in the safety profile of oxybutynin when formulated as a CR (Gupta et al., 1999; Sathyam et al., 2001).

Despite the fact that clinical evidence might support the aforementioned hypothesis, there are no clear indications whether this higher relative bioavailability would be observable for all CYP3A substrates when formulated as CR. Due to the complex relationship between absorption and first pass metabolism in the GI tract (Darwich et al., 2010) it might prove difficult to differentiate the main driving forces behind this observed phenomenon, i.e., colonic absorption window vs. a decreased gut wall metabolism in the colon, or both (Tannergren et al., 2009). To our knowledge however there is a paucity of studies investigating these bioavailability differences in a prospective manner. In addition, no attempts have been made to either elucidate the drug and formulation properties associated with the occurrence of such phenomenon or to correlate its magnitude to the aforementioned drug’s physicochemical, biochemical and biological properties.

Due to the multifactorial nature of the problem, modelling and simulation (M&S), in particular physiologically-based pharmacokinetic (PBPK) M&S, can be useful for the prospective analysis of the impact of such properties on the absorption and first pass metabolism of CR formulations of CYP3A substrates. In silico PBPK models integrate current knowledge of both the system, i.e., morphophysiological factors and their population characteristics) and drug properties that may influence oral drug absorption (Jamei et al., 2009c). This approach has the advantage to allow the theoretical exploration of the interplay between the system and the drug properties and therefore hypothesize on the main driving forces that control drug absorption, transport and metabolism (Darwich et al., 2010).

Herein the relative bioavailability between CR and IR formulations of CYP3A substrates was investigated in order to understand how the physicochemical, biochemical and pharmaceutical properties of a drug (or drug product) can affect its oral bioavailability. Firstly, a literature survey was performed to collate clinical studies in which the pharmacokinetics of CYP3A4 substrates were simultaneously investigated in both IR and CR formulations. Secondly, a systematic analysis was performed to investigate the impact that drug release characteristics and the drug-related physicochemical
and biochemical properties defining oral bioavailability have on oral drug absorption and CYP3A4-mediated intestinal first pass metabolism. This was performed using in silico PBPK M&S. The aims of this study were to investigate possible mechanisms involved in the observed differences in oral bioavailability between IR and CR formulations by analysing the trends in $f_	ext{a}$, $F_	ext{rel}$, and the systemic exposure (AUC). In addition, an attempt was made to identify the parameter space associated with the higher relative bioavailability of drugs formulated as CR compared to their IR counterparts and to correlate simulations with the observed clinical data gathered from the literature search.

2. Materials and methods

2.1. Literature survey

A literature survey was conducted using PubMed and Google Scholar in order to identify studies in which the pharmacokinetics of CYP3A4 substrates formulated as IR and CR was investigated. The search was restricted only to those studies in which the pharmacokinetic parameters of both formulations were investigated in the same set of subjects, ideally healthy adult volunteers. In order to avoid any possible food effects on the absorption parameters, only studies for which the formulations were administrated in fasted conditions were considered. The main pharmacokinetic parameter of interest was the AUC. Whenever reported, the relative bioavailability between the IR and CR formulation, in terms of the AUC ratio (CR/IR) and its 90% confidence interval was employed. Otherwise it was calculated employing an approximation of the Fieller’s Theorem (Fieller, 1954; Motulsky, 2010) using the reported AUCs, only when both CR and IR formulations were investigated in the same set of subjects. The detailed calculation method is described in the Supplementary Material.

2.2. Simulations and PBPK model

For the analysis of the impact of the controlled release formulations on $f_	ext{a}$, $F_	ext{rel}$ and systemic exposure, a series of simulations were conducted employing the Advanced Dissolution Absorption and Metabolism (ADAM) model within the Simcyp® population-based simulator (Jamei et al., 2009b) Version 12 Release 2 (Simcyp Limited, Sheffield, UK). The ADAM model is a PBPK absorption model that integrates the drug physicochemical and biopharmaceutical properties (e.g. release profile, solubility, permeability, particle size, affinity for metabolic enzymes, etc.) and the human physiology (e.g. gastric emptying, intestinal transit times, GI fluid volumes, metabolic enzyme abundances, blood flows, bile secretion, etc.) and their variability (Jamei et al., 2009b, 2009c). Within the ADAM model the anatomy of the human GI tract is represented by nine consecutive segments (stomach, duodenum, jejunum 1 and 2, ileum 1–4, and colon). Each segment is described as a smooth cylinder with the anatomical and physiological characteristics of each segment accounted for, i.e., fluid dynamics, pH, bile salt concentration, surface area, blood flows, gut wall mass and volume, etc. Drug transit through the segments is modelled as first order unidirectional process, from the stomach to the colon. In each segment the amount of drug is distributed between four different states: drug in formulation, drug released (undissolved), drug dissolved, and drug degraded in the lumen. The dissolution rate can either be inputted from an in vitro dissolution profile and/or estimated from a built-in diffusion layer model (DLM), it is assumed that only dissolved drug can be absorbed. Drug absorption into the gut wall is modelled as a first order process depending on the drug’s intestinal permeability and the segment’s physiological characteristics. When required, Michaelis–Menten kinetics can be used to model carrier mediated intestinal uptake and/or efflux. The intestinal regional distribution pattern of a given transporter is incorporated and is expressed relative to the abundance in the jejunum (Mouly and Paine, 2003; Jamei et al., 2009c). It is also assumed that the absorption from the stomach is negligible compared to the absorption in the small intestine and the colon. The drug is absorbed into the enterocyte compartment, where enzymatic first pass metabolism can occur by either CYPs and/or UDP-glucuronosyltransferases (UGTs), following Michaelis–Menten kinetics; with only the drug’s free fraction (fraction unbound ($f_	ext{a}$)) being susceptible to metabolism. Alternatively, the $Q_{out}$ model (Yang et al., 2007) can be employed for the estimation of the first pass gut wall metabolism. The distribution of CYPs and UGTs enzymes along the GI tract is also incorporated in the ADAM model. The non-metabolized fraction enters the portal vein by means of blood flow limited processes and subsequently enters the liver, where additional first pass metabolism can occur prior to reaching the systemic circulation. A detailed description of the ADAM model within the Simcyp® population-based simulator can be found elsewhere (Jamei et al., 2009b,2009c). The selection of the ADAM model was based on its capability to simulate drug absorption and first pass metabolism, taking into account the factors that have an impact on these processes.

2.3. Study design and parameter selection

To investigate the impact of different formulations and the relevant drug properties on $f_	ext{a}$, $F_	ext{rel}$ and AUC a factorial study was designed (Fig. 1). A set of five release profiles, representative of five different formulations, were defined by varying the release rate constant ($k_{rel}$) from 0.096 h$^{-1}$ to 4.6 h$^{-1}$ in Eq. (1)

$$F_{rel}(t) = 1 - e^{-k_{rel}t}$$

where $F_{rel}(t)$ is the fraction of the dose released from the formulation as a function of time (h). The five release profiles were representative of two immediate release (IR) tablets and three controlled release (CR) tablets. The profiles were designed to release 90% of the drug content within 0.5, 1, 6, 12 and 24 h, resulting in a $k_{rel}$ of 4.6, 2.3, 0.38, 0.19, and 0.096 h$^{-1}$, respectively ($t_{50}$). Six drug-specific parameters were selected based on their importance in defining oral bioavailability and were systematically modified to generate a set of virtual compounds. The modified parameters included: solubility (mg/mL); human jejunal effective permeability, $P_{eff}$ (10$^{-4}$ cm/s); maximal CYP3A4-mediated metabolic rate, $V_{max,CYP3A4}$ (pmol/min/mg microsomal protein); CYP3A4 affinity, $K_{m,CYP3A4}$ (μM); maximal P-gp-mediated efflux rate, $J_{max,p,g}$ (pmol/min); and P-gp affinity, $K_{m,p,g}$ (μM). In addition, each parameter was assigned five different values. Hence, the number of virtual compounds amounted to 15,625. For each virtual compound five simulations were carried out, one for each of the release profiles described above, resulting in a total of 78,125 simulations (5)$^7$. The specific ranges for each parameter were derived from the literature and were representative of the values obtained experimentally. Unless otherwise stated, the values were representative of approximately the 1st, 25th, 50th, 75th and 99th percentile of the range reported in the selected references.

Aqueous solubility values were derived by rearranging the dose number ($D_0$) equation (Amidon et al., 1995) into Eq. (2), and employing the $D_0$ values as reported by Benet et al. (2011), only for the compounds for which the authors reported the experimental aqueous solubility. The dose employed for the estimation of the solubility as function of the $D_0$ was 30 mg. The reason for selecting this dose was based on an exploratory study initially performed for buspinore, where administered the dose for the CR formulation was 30 mg (Sakr and Andheria, 2001a,2001b). The aforementioned
Dose values within and and and values were con-
values using the default method in the
and in the ADAM model, using the same equation.
assuming linear conditions. Limitations were
values were estimated from
range was obtained using
values were limited, when possible,
to those that in combination generated Clint, CYP3A4 values within
the Clint, CYP3A4 range reported by Bu (2006).

Transporter kinetic parameters, i.e., Jmax and Km, for the P-gpmediated efflux in Caco-2 cell monolayers were obtained from
the work of Troutman and Thakker (2003) for 8 different P-gp
substrates. In the same way as for the CYP3A4 kinetic parameters,
P-gp-related parameters were treated as independent, and
the intrinsic clearance (Clint, P-gp) was calculated from the ratio
between Jmax and Km assuming linear conditions. Limitations were
applied as described above to match the reported Clint, P-gp values (Troutman and Thakker, 2003).

2.4. Model assumptions and simulations

A Simcyp "compound file" was created based on the reported
physicochemical characteristics, protein binding and blood-to-
plasma ratio for the compound buspirone (Gammans et al., 1986;
Gertz et al., 2011; Shibata et al., 2002). The "compound file" was
then modified and used as a template to generate a set of virtual
compounds from the combinations of the aforementioned param-
eters. The ionic class of the virtual compounds was set to be neu-
tral in order to simplify the analysis and to reduce the number of
combinations that could be derived from accounting for the differ-
ent ionic classes. The drug’s dissolution rate was estimated using
the diffusion layer model built into the Simcyp® ADAM model,
where the drug was assumed to be a monodispersed powder with
an initial particle radius of 30 μm. Papp values were estimated from
the calculated Papp,Caco-2 values using the default method in the
Simcyp® simulator for passively absorbed drugs (Sun et al.,
2002). Peff was kept constant throughout all the intestinal seg-
ments. Elimination was assumed to occur only by means of
CYP3A4-mediated metabolism, both in the liver and the GI tract,
which was estimated from the aforementioned enzyme kinetics
parameters of CYP3A4. The fraction of drug unbound in the enterocytes (fu,gut) was assumed to be 1 as per Yang et al. (2007). The rest
of the parameters were kept as Simcyp® default values. The input
parameters are summarized in Table S1 of the Supplementary
Material.

The virtual trials were simulated assuming a representative
population. The values employed were those from the “healthy
volunteers” population library within Simcyp®, assuming no vari-
ability for the system parameters. A “minimal” PBPK model was
used to describe the disposition and systemic elimination of the
simulated compounds (Rowland Yeo et al., 2010). The oral dose
was set to 30 mg, administered under fasted conditions together
with 250 mL of water; with sampling up to 36 h post dose (Sakr
and Andheria, 2001a, 2001b). Simulations were carried out using
the Simcyp® Batch processor on a Dell OptiPlex 7010 PC (Intel Core
i7-3770, 16 GB Ram) running Microsoft Windows 7 Enterprise
(Dell Corp. Ltd., Berkshire, UK).

2.5. Data analysis

In order to analyse the simulated data the study tree was sub-
categorized into the four classes described in the BCS, thus leading
to a reduction in the number of combinations analysed (from 78,125 to 12,500) by limiting the values for solubility and permeability from five to two values each. Selection of the solubility and permeability values was based on the BCS cut-off criteria for high/low soluble and permeable compounds. Solubility was considered high if its corresponding $D_n$ was less than 1, whereas for a $D_n$ equal or greater than 1, solubility was considered as low (Amidon et al., 1995). Permeability was considered high if the calculated fraction absorbed was equal or greater than 0.9, and a value below 0.9 was considered as low permeability (U.S. Food and Drug Administration, 2000). The fraction absorbed was calculated employing Eq. (4) (Amidon et al., 1995; Sinko et al., 1991)

$$f_a = 1 - e^{-\frac{V_{\text{app},Caco-2}}{n\cdot6\cdot\text{cm/s}}}$$ (4)

where $R$ is the mean radius of the small intestine (1.75 cm) and $T_{50}$ is the mean transit time in the small intestine (3.32 h) (Lennernäs et al., 1992; Yu et al., 1996).

Data analysis was carried out using Matlab 2013a (The Mathworks Inc., Natick, MA, USA). The analysis was focused on the impact of the release rate constant ($k_{rel}$), and the drug specific parameters on the simulation outcome ($f_a$, $F_{rel}$ and AUC). Several scenarios were evaluated for the impact of both CYP3A4 and P-gp clearance employing a "one-at-a-time" method, i.e., fixing most of the parameters and varying the parameters of interest. These were accomplished by either fixing $V_{\text{max,CYP3A4}}/V_{\text{max,P-gp}}$ and varying $K_m$ (CYP3A4/P-gp) or vice versa. The scenarios evaluated are described in Table 1.

Amongst the scenarios described in Table 1, the cases in which a CR formulation showed higher relative bioavailability ($F_{rel}$) than the corresponding IR formulation were investigated in further detail. $F_{rel}$ was calculated using Eq. (5)

$$F_{rel} = \frac{AUC_{CR}}{AUC_{IR}} \times 100$$ (5)

where $AUC_{IR}$ was the AUC of the IR formulation with a $k_{rel}$ of 4.6 h$^{-1}$ and $AUC_{CR}$ was the AUC of any of the other formulations evaluated. The simulations were compared, in terms of release characteristics, relative bioavailability and metabolic clearance, with the observed data derived from the literature search. The latter was performed only for compounds with similar physicochemical properties as the simulated compounds and for those for which the main metabolic enzyme was CYP3A4, i.e., the CYP3A4 is responsible for 50% or more of the compound’s metabolic clearance ($f_{\text{m,CYP3A4}} > 0.5$). Whenever possible the release characteristics of the literature compounds were derived from the in vitro release profiles where the corresponding $k_{rel}$ was estimated according to its $t_{50}$ (Eq. (6)) otherwise these were approximated based on the information described in the product label and/or clinical studies. With regards to the metabolic clearance, in order to avoid any possible underpredictions resulting from the use of the mean in vitro metabolic data (Hallifax et al., 2010; Hallifax and Houston, 2012) the intrinsic metabolic clearance in HLM was back calculated from the in vivo systemic clearance employing either the well-stirred model (Rowland et al., 1973) or the dispersion model (Roberts and Rowland, 1986). The details of the calculations are described in the Supplementary Material.

$$k_{rel} = \ln 10 \frac{T_{50}}{D_n}$$ (6)

3. Results

The literature survey was successful in retrieving and identifying 17 studies of 11 different compounds that met the inclusion criteria (Fig. 2). The compounds were identified to belong to classes 1–3 of the BCS. Based on the 17 studies uniquely identified in this investigation, 23 data points were derived for the analysis of the relative bioavailability between CR and IR formulations, 8 of which were directly given in the reports whilst the rest were calculated from the information given in the reports. The detailed information in terms of AUC ratios, 90% confidence intervals and their references are shown in Table S2 of the Supplementary Material.

3.1. Parameter range and values

The simulated parameters and their ranges are summarized in Table 2. Solubility varied from $10^{-5}$ to $10^4$ mg/mL as derived from Eq. (2). The range of solubility values was truncated to a minimum of 0.001 mg/mL and a maximum of 100 mg/mL in order to improve the computational performance of the simulations. Human $P_{app}$ ranged from 0.04 to 10 $\times 10^{-4}$ cm/s. Calculated $P_{app,Caco-2}$ values (Eq. (3)) varied from 0.01 to 80 $\times 10^{-6}$ cm/s, covering the range from low to highly permeable compounds (Lennernas, 2007). The $V_{\text{max,CYP3A4}}$ and $K_m,CYP3A4$ range varied from 1 to 10,000 pmol/min/mg microsomal protein and 1–100,000 μM, respectively. $J_{\text{app},P-gp}$ and $K_m,P-gp$ ranges were 1–1500 pmol/min and 1–2,000 μM, respectively.

3.2. Cut-off values for BCS classification

The values that defined the limits for high and low solubility were 10 mg/mL ($D_n = 1.2$) and 1.0 mg/mL ($D_n = 0.12$), respectively. Likewise, the value for high permeability was 5 $\times 10^{-6}$ cm/s ($f_a \approx 0.89$) whereas for low permeability, the value was 0.5 $\times 10^{-6}$ cm/s ($f_a \approx 0.34$). For both solubility and permeability, the selected cut-off values coincided with the 25th and 50th percentile of their selected range (values 2 and 3 in Fig. 1).

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Description</th>
<th>$V_{\text{max,CYP3A4}}$ (μL/min/mg)</th>
<th>$J_{\text{app},P-gp}$ (μL/min/mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>la</td>
<td>CYP3A4 (m)</td>
<td>Fixed (500)</td>
<td>–</td>
</tr>
<tr>
<td>lb</td>
<td>CYP3A4 (m)</td>
<td>Variable</td>
<td>–</td>
</tr>
<tr>
<td>Ia</td>
<td>CYP3A4 (m)</td>
<td>Fixed (2500)</td>
<td>–</td>
</tr>
<tr>
<td>Ib</td>
<td>CYP3A4 (m)</td>
<td>Variable</td>
<td>–</td>
</tr>
<tr>
<td>IIIa</td>
<td>P-gp (m)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>IIIb</td>
<td>P-gp (m)</td>
<td>–</td>
<td>Variable</td>
</tr>
<tr>
<td>IVa</td>
<td>CYP3A4 (h)</td>
<td>Fixed (2500)</td>
<td>Variable</td>
</tr>
<tr>
<td>IVb</td>
<td>CYP3A4 (h)</td>
<td>Variable</td>
<td>Fixed (1)</td>
</tr>
<tr>
<td>Va</td>
<td>CYP3A4 (h)</td>
<td>Fixed (2500)</td>
<td>Fixed (1)</td>
</tr>
<tr>
<td>Vb</td>
<td>CYP3A4 (h)</td>
<td>Fixed (2500)</td>
<td>Variable</td>
</tr>
</tbody>
</table>

(h), high; (m), medium.
was kept fixed (scenarios Ia and IIa compared to the IR formulations, (Figs. 4B and S4B). Since had no impact on in had an impact on the resulted in a small increase on the had an impact on decreased when moving from BCS class 1 to class 4.

and using a fixed CLint,CYP3A4 equal to or greater than 200 was lower of BCS class 2 compounds was the showed an opposite trend as compared in scenario IIb, i.e., high affinity were almost imperceptible (Figs. 3B and S1B–S2B). On values between 0.007 and 30 was fixed to the 'medium' value (scenario Ib in Table 1) though the CLint,CYP3A4 similar change in exposure was reduced to 50 l

In general, a reduction in release rate, i.e., changing from an IR formulation to a CR formulation, was associated with a decrease in AUC for a majority of the CYP3A4 substrates (Figs. 3A and S1A–S3A). However, in certain cases, the AUC remained constant for CR formulations of highly cleared BCS class 1 compounds, CLint,P-gp was higher for highly permeable compounds (BCS classes 1 and 2). On the contrary, Fc showed an opposite trend as compared to that of fe. The CR formulations showed higher Fc than their IR counterparts, the increase was inversely related to the decrease in drug release rate. The magnitude of the increase in Fc was dependent on the CLint,CYP3A4 and was typically observed for virtual compounds with CLint,CYP3A4 equal to or greater than 200 l/min/ mg. For compounds displaying a low affinity to CYP3A4, the differences in Fc were almost imperceptible (Figs. 3B and S1B–S2B). On the contrary, for compounds with high affinity for CYP3A4, the difference in Fc as a function of both release rate and CLint,CYP3A4 was highly marked (scenario IIb; Fig. S3B).

3.4. Simulations: P-gp substrates

For the simulated P-gp substrates (scenarios IIIa and IIIb in Table 1) the relationship between AUC and drug release was similar to that observed for the CYP3A4 substrates. Nevertheless, irrespective of the values for CLint,P-gp, the AUC decreased as the release rate was reduced, this was more pronounced for low soluble compounds (BCS classes 2 and 4; Figs. 4A and S4A). For BCS class 1 compounds, CLint,P-gp values between 0.007 and 30 l/min had almost no impact on the AUC. However, a decrease in the AUC was observed when CLint,P-gp was set to 300 l/min (Figs. 4A and S4A). No differences were noticeable when fixing either Jmax,P-gp or Km,P-gp. As for the CYP3A4 substrates, the fe was lower for CR formulations than for their IR counterparts, and decreased as the release rate decreased. On the contrary to what was seen for CYP3A4 substrates, altering CLint,P-gp had an impact on the fe, where the impact on fe was dependent upon the CLint,P-gp values and BCS classification. The fe of BCS class 2 compounds was the most sensitive to changes in CLint,P-gp (Figs. 4B and S4B). Since the aforementioned compounds were not subject to metabolism, neither the release rate nor the CLint,P-gp had an impact on Fc.

3.5. Simulations: CYP3A4 and P-gp substrates

Scenarios IVa–Vb in Table 1 describe the simulations carried out for virtual compounds with overlapped affinity for both CYP3A4 and P-gp. When CLint,CYP3A4 was varied, and using a fixed CLint,P-gp (2 l/min), no significant differences were observed between the new AUC trend compared to the trend observed for CYP3A4 substrates only (Figs. 5A and S5A). A similar outcome was obtained when the analysis was performed from the P-gp point of view, i.e., varying CLint,P-gp and using a fixed CLint,CYP3A4 (2500 l/min/mg); the observed trends were similar to that for P-gp substrates alone (Figs. S6–7B). Likewise, both fe and Fc followed almost a similar pattern as the observed for CYP3A4 or P-gp substrates only (Figs. 5B and S5–7B). Although the overall trend remained the same, subtle changes were observed in the trends of fe and Fc in response to changes in the CLint,CYP3A4 or CLint,P-gp, respectively; an increase of CLint,CYP3A4 led to an increase in fe (Fig. 5B), likewise, an increase in CLint,P-gp resulted in a small increase on the Fc (Figs. S6–7B). These changes were dependent of both release rate and BCS classification, as the increase in fe was more prominent for IR formulations of BCS class 2 compounds (Figs. 5B and S5B).
whereas the impact of CLint,P-gp on FG was perceptible only for IR formulations of BCS class 1 compounds (Fig. S6A).

3.6. Relative bioavailability of CYP3A4 substrates

Analysis of the relative bioavailability (Frel) of CR formulations showed that highly (CYP3A4) cleared BCS class 1 simulated compounds could display up to a 220% higher Frel compared to the IR formulations. When the trends for the simulations were compared with similar compounds derived from the literature survey, i.e., BCS class 1 and mainly CYP3A4 cleared, there was a very good agreement between the simulated Frel and the observed data (Fig. 6). The back-calculated CYP3A4 clearance values (HLM) from the in vivo systemic clearance are reported in Table S3 of the Supplementary Material.

4. Discussion

4.1. Analysis of the relative bioavailability between CR and IR formulations of CYP3A4 substrates

Due to the selected inclusion criteria for the search, the analysis was limited only to 11 different compounds (Fig. 2). A larger set of drugs could have been included for this analysis if, for instance, the calculations of relative bioavailability were performed between different subjects and groups, i.e., the IR data was taken from one study whereas the CR data was taken from a separate study. However, this would have confounded the impact of the formulation with the inter-individual variability of the kinetics, leading to variable Frel. Therefore these studies were not considered. Of the total drugs investigated, only three drugs formulated as CR showed statistically significant higher relative bioavailability than their IR formulations (simvastatin, buspirone and oxybutynin). In contrast, a majority of the drugs showed either similar or lower relative bioavailability when formulated as CR. Judging from the BCS point of view an a priori trend for either higher or lower Frel was not clear. For instance CR formulations of fluvastatin (BCS class 1) and simvastatin (BCS class 2), both highly permeable compounds, showed opposite results in terms of Frel (Fig. 2). Whereas CR formulations of low permeable compounds, such as propiverine and gepirone (both BCS class 3), showed similar Frel to their IR formulations. Therefore this justified the use of more mechanistic and multivariate models such as PBPK for M&S purposes in order to accommodate several factors influencing the observed differences.

4.2. Impact of release rate on oral drug absorption and bioavailability

A general trend towards a reduction in drug exposure (AUC) was observed in simulations when varying the release rate, i.e., moving from an IR formulation to a CR formulation. These results were anticipated as, in general the CR formulations are intended to release the majority the drug content further distally in the intestine (e.g., distal ileum and colon), where the distal regions of the GI tract provides unfavourable conditions for drug absorption compared to the upper regions of the GI tract. This assumption is supported by the observed decrease in fa when switching from IR to CR formulations (Figs. 3–5B). Interestingly the decrease in fa was observed for all the scenarios evaluated irrespectively of BCS class, CYP3A4 clearance, and/or P-gp efflux. These results are in line with the work by Tannergren et al. (2009), where they investigated the colonic absorption and bioavailability of several compounds, compared to that in upper regions of the GI tract. For BCS class 1 compounds, the relative
Fig. 4. Impact of release rate (formulation) and CL\textsubscript{int, P-gp} on AUC (A), f\textsubscript{a} and F\textsubscript{G} (B) for non CYP3A4 substrates. J\textsubscript{max, P-gp} was fixed at 300 pmol/min whereas the K\textsubscript{m, P-gp} was varied (scenario IIIa in Table 1). For plots A and B, the subplots represent the different BCS classes (1–4), whereas the symbols in each plot represent different CL\textsubscript{int, P-gp} values: upper triangle (300), circle (6), square (2), diamond (1), and lower triangle (0.15). For the plots in the right hand side (B), the green lines and open symbols represent the F\textsubscript{G}, whereas the black lines and filled symbols represent the f\textsubscript{a}. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Fig. 5. Impact of release rate (formulation), CL\textsubscript{int, CYP3A4} and CL\textsubscript{int, P-gp} on AUC (A), f\textsubscript{a} and F\textsubscript{G} (B). V\textsubscript{max, CYP3A4} was fixed at 2500 pmol/min/mg whereas the K\textsubscript{m, CYP3A4} was varied (scenario Va in Table 1). CL\textsubscript{int, P-gp} was fixed to 2 lL/min. For plots A and B, the subplots represent the different BCS classes (1–4), whereas the symbols in each plot represent different CL\textsubscript{int, CYP3A4} values: upper triangle (2500), circle (250), square (50), diamond (25), and lower triangle (0.25). For the plots in the right hand side (B), the green lines and open symbols represent the F\textsubscript{G}, whereas the black lines and filled symbols represent the f\textsubscript{a}. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
colonic bioavailability was considered good compared to that in the upper regions of the intestine. In this study the $F_{\text{rel}}$ between the IR and CR formulations for low CYP3A4 affinity BCS class 1 compounds, varied between 49% and 80% (mean: 66%) in agreement with the value reported by Tannergren et al. (2009) ($F_{\text{rel}}\geq 70\%$). On the other hand, the simulated relative absorption, $f_{\text{a,rel}}$, for the same compounds varied between 66% and 88% (mean: 72%). Where Tannergren, and co-workers, reported values between 39% and 127% with a mean of 82% (Tannergren et al., 2009). For BCS classes 3 and 4, however, Tannergren found a low $F_{\text{rel}}$ in the colon ($F_{\text{rel}} < 50\%$). In the current simulation study, $F_{\text{rel}}$ varied between 42% and 68% for BCS class 3 compounds, and 23% and 53% for BCS class 4 compounds, whereas $f_{\text{a,rel}}$ varied between 58–76% and 34–61% for BCS classes 3 and 4 compounds, respectively. The latter might indicate an overestimation of the absorption for BCS classes 3 and 4 compounds in our simulations. This could be due to an overestimation of colonic permeability, in our study we employed a constant $P_{\text{eff}}$ value throughout all intestinal segments within the ADAM model, however this might not be necessarily the case. It has been suggested that the reduced surface area and increased number of tight junction in the colon could limit the permeability of passively absorbed compounds (Lennernas, 2014a), thus permeability could vary along the GI tract, in particular for the colon. This was not taken into account in the simulations, and could lead to this possible overestimation of $f_{\text{a,rel}}$. Nevertheless, more data has been sought in order to support the existence of a differential permeability along the GI tract (Lennernas, 2014b). Another possible source of error that might explain those differences was the use of Eq. (3) to correlate $P_{\text{app,Caco-2}}$ with $P_{\text{eff}}$ (and vice versa). This equation is associated with large prediction intervals and therefore this can affect the $P_{\text{eff}}$ predictions (Sun et al., 2002). However this is unlikely to affect the overall outcome of this study as the values $P_{\text{app}}$ values were subsequently back-transformed into $P_{\text{eff}}$ using the same equation by the ADAM model.

A similar overestimation could arise for colonic solubility. In the present study all compounds were treated as neutral and therefore regional differences in the intestinal pH, which are accounted for in the ADAM model, did not affect intestinal solubility of the compounds. This may in particular lead to an overestimation of colonic solubility of basic compounds, whereas an opposite situation can occur for acidic compounds, for which the solubility is higher in the upper regions of the GI tract. There are also many in vivo factors that might contribute to the possible under/overestimation of drug dissolution and solubility within the GI tract. For instance the oversimplified composition of the small intestinal and colonic fluids in available PBPK absorption models, as well as the actual fluid volumes available to dissolve the drug might affect such estimations (Sjogren et al., 2014).

Furthermore, several biopharmaceutical and physicochemical properties, known to influence drug absorption, were not taken into account in this study, i.e. particle size and its distribution; excipients; and in particular the drug release mechanism, which was oversimplified in this study; just to name a few (Martinez and Amidon, 2002). Consideration of such factors would have significantly increased the number of simulations to be performed, thus complicating any subsequent analysis. Those simulations were out of the scope of this work.

4.3. Understanding of the higher relative bioavailability observed for CR formulations of CYP3A4 substrates

One of the main goals of this work was to identify the parameter space in which a drug, formulated as CR, would display higher

![Graph showing the impact of release rate and CLint,CYP3A4 on the relative bioavailability (%) for BCS class 1 compounds. The figure includes a 3D surface and a color bar indicating the $F_{\text{rel}}$ values (%). The circles and line represent the mean $F_{\text{rel}}$ and its 90% confidence interval for BCS class 1 compounds mainly cleared by CYP3A4 ($fm_{\text{CYP3A4}}\geq 0.5$): buspirone sustained release (BUSP F1), buspirone extended release (BUSP F2), oxybutynin extended release (OXYB), quetiapine extended release (QETP) and cyclobenzaprine extended release (CBZP).]
relative bioavailability than the corresponding IR formulation. The above results clearly indicated absorption – \( f_a \) – to be reduced for all the CR formulation as compared to the IR formulations. Still, in the case of the simulated CYP3A4 substrates, the reduction in \( f_a \) seemed to be compensated by an increase in \( F_r \) (Figs. 3B and S1B–S3B), that is, a reduction in the CYP3A4-mediated first pass intestinal metabolism. For some of the simulated compounds, this compensation was translated into similar exposure levels of CR formulations as compared to IR. The proposed explanation is based on the distribution of the CYP3A4 abundance along the GI tract. As discussed previously in this manuscript, the CYP3A enzymes decrease towards the distal regions of the human GI tract (Berggren et al., 2007; Paine et al., 1997; Zhang et al., 1999), this pattern is taken into account in the ADAM model. As a result, when a CR formulation releases its drug content into the distal regions of the intestine, the drug would encounter less CYP3A4 enzymes on its way towards the portal circulation, thus reducing the CYP3A4-mediated intestinal first pass metabolism. In this study the impact on the AUC was however only noticeable for highly permeable (BCS classes 1 or 2) and highly cleared drugs (\( \text{CL}_{\text{int,CYP3A4}} \geq 2500 \mu L/min/mg \)). This seems reasonable as the differences in absorption between CR and IR formulation, for BCS classes 2 and 4 compounds, would be too high to be compensated by a reduction in the intestinal first pass metabolism. Nevertheless, a similar exposure level as the IR formulation was observed for the CR formulations for some of the BCS class 3 compounds (high \( \text{CL}_{\text{int,CYP3A4}} \geq 2500 \mu L/min/mg \)). This could be a product of the aforementioned overestimation in absorption. BCS class 1 compounds, on the other hand, are more likely to be absorbed in distal regions of the GI tract (Tannergren et al., 2009). Thus, for this type of compounds, the reduction in intestinal metabolism could lead to AUC levels higher than that observed for IR formulations (Figs. 3A and S3A).

A relative bioavailability of up to 220% was observed for the simulated CR formulations of highly CYP3A4-cleared compounds (\( \text{CL}_{\text{int,CYP3A4}} \geq 2500 \mu L/min/mg \)) (Fig. 6). These results were in good agreement with the clinical observations for CR release formulations, for buspirone, oxybutynin, quetiapine and cyclobenzaprine, where the increase in relative bioavailability in the CR formulations was dependent upon an apparent reduction in metabolic clearance of the aforementioned compounds. The use of \( \text{in vivo} \) data for the determination of the \( \text{in vitro} \) intrinsic clearance for the analysis in Fig. 6 seemed justified as the \( \text{in vitro} \) values would have underpredicted the \( \text{in vivo} \) clearance for oxybutynin and buspirone. The \( \text{in vitro} \) clearance, varied between 268 and 442 \( \mu L/min/mg \) (Gertz et al., 2011; Zhu et al., 2005) for buspirone, and 78–278 \( \mu L/min/mg \) for oxybutynin (Mizushima et al., 2007; Yaich et al., 1998), whereas the value determined from the \( \text{in vivo} \) clearances (Table S3) were 5454 \( \mu L/min/mg \) and 2932 \( \mu L/min/mg \) for buspirone and oxybutynin, respectively. This underprediction was also observed, to a lesser extent, for cyclobenzaprine, whereas for quetiapine an \( \text{in vitro} \) value similar to the \( \text{in vivo} \) value was observed (Table S3). The mechanisms behind said underpredictions when using human liver microsomes are still unknown; however it has been attributed to factors such as the ionization, binding to plasma proteins, and clearance model inaccuracies (Berezhkovskiy, 2011; Hallifax et al., 2010; Hallifax and Houston, 2012; Poulin, 2013; Poulin et al., 2012). Simvastatin (BCS class 2) represent an interesting case that was not in agreement with the simulated \( F_{ha} \) across the defined parameter space. Even though simvastatin is classified as BCS class 2 the CR formulation showed 2–3-fold higher relative bioavailability that the IR formulation. One of the reasons for such disagreement with the simulated data was the use of an enabling CR formulation in one of the simvastatin studies (Tubic-Grozdanis et al., 2008). The formulation employed in the aforementioned study contained a mixture of gelatine and lecithin intended to improve the wettability of simvastatin in the formulation and promote the formation of microemulsions or even micelles, thus improving simvastatin's dissolution. In fact, the solubility of simvastatin was increased more than 5000 times when it was embedded in the mixture of gelatine and lecithin (Tubic-Grozdanis et al., 2008). It is not clear whether the CR formulation employed in the study by Jang et al. (2010) used the same approach to increase the solubility of simvastatin. Yet, the exposure of the CR formulation was similar to that of Gertz et al. (2010; Tubic-Grozdanis et al., 2008).

Another factor that might have influenced the observed differences in simvastatin's exposure between IR and CR formulations can be the fact that simvastatin is a prodrug that is converted to simvastatin acid (the active form) \( \text{in vivo} \) (Prueksaritanont et al., 2005). This process can occur by means of chemical and enzymatic hydrolysis in both the gut wall and lumen, therefore differences the enzyme levels along the gut wall membrane could explain some of the observed differences in simvastatin's exposure (Alvarez-Lueje et al., 2005; Prueksaritanont et al., 2005; Satoh et al., 2002). However, due to the similar exposure observed for simvastatin acid between the IR and CR formulations, we believe that these differences are predominately due to differences in the CYP3A4-mediated metabolism of simvastatin (Jang et al., 2010; Tubic-Grozdanis et al., 2008). Another aspect of this simulation study that may result in discrepancies between simulated and observed data is the attempt to describe a hypothetical BCS class 1 drug. However, the physiochemical, biopharmaceutical, and affinity properties employed herein were not necessarily intended to represent those for the drugs used for the comparison (i.e., oxybutynin, buspirone, etc.). Finally, in our study, the fraction of drug unbound in the enterocytes was assumed to be 1. This assumption can affect \( F_r \) estimations, as only the free drug concentration in the enterocyte would be available for metabolism (Darwich et al., 2010; Heikinnen et al., 2012; Sinha et al., 2012). This parameter is highly sensitive and this might affect the results of the simulations when there is binding to the enterocytes (Gertz et al., 2010; Yang et al., 2007). Nevertheless, this was not the case, as the simulations performed herein were not meant to represent any particular compound, rather they were representative of hypothetical cases, and thus the \( \text{CL}_{\text{int,CYP3A4}} \) range should be considered as an unbound intrinsic clearance.

4.4. Impact of the intestinal P-gp distribution and possible CYP3A4/P-gp interplay on the bioavailability of CR formulations

The results for the simulated P-gp substrates were consistent with the previous work by Darwich et al. (2010). In general both absorption and exposure were decreased when \( \text{CL}_{\text{int,P-gp}} \) was increased. No impact on \( F_C \) was observed as function of the \( \text{CL}_{\text{int,P-gp}} \), in this scenario no intestinal metabolism was considered. In addition, no significant differences in terms of absorption and exposure were observed between the IR and CR formulations as product of variable P-gp clearance (Fig. 4).

When the analysis was performed on compounds with overlapped affinity for both CYP3A4 and P-g, no significant differences were observed in the trend for AUC compared to that of simulated CYP3A4 or P-gp substrates alone (Fig. 5). In the same line, only minor differences in the trends for \( f_a \) and \( F_r \) were observed. These subtle differences might be an indication of a possible competition between CYP3A4 and P-gp for the substrate in the enterocyte compartments within the ADAM model. However, the reasons for such differences are not clear yet. Further discussion about these results is included in Sections 5 and 6 of the Supplementary Material.
4.5. Similar studies and the use of PBPK model for formulation development

Previous multi-scale studies have investigated the complex interplay between the factors governing drug absorption and intestinal first-pass metabolism and absorption such as the study by Darwich et al. (2010), using the same ADAM model, or the study by Heikkinen et al. (2012) using the Advanced Compartmental Absorption and Transit (ACAT) model in Gastroplus™. Nevertheless, to our understanding, this is the first study that has investigated the impact of the release characteristics from the formulation on oral bioavailability, specially focused on the interplay between the physicochemical, biopharmaceutical and biochemical properties.

From a biopharmaceutics point of view, there are an increasing number of examples of the use of PBPK models for the optimization of new dosage forms, in particular for CR formulations. Some of these examples have recently been reviewed by Brown et al. (2012). The use of PBPK models for the evaluation of the impact of biopharmaceutical properties on absorption has recently been encouraged by the regulatory agencies such as by the United States Food and Drug Administration (Zhang and Lionberger, 2014). In addition, our study provides a systematic analysis of the available data on the relative bioavailability of CYP3A4 substrates as well as the impact of drug- and formulation-specific factors on the oral bioavailability. The outcome of this study can be considered as a first step in the line of providing examples of possible applications of PBPK M&S in the formulation development process, in particular for the evaluation of the possible impact of controlled release dosage forms on the drug candidate’s absorption and bioavailability. This applies in particular for drugs candidates that are considered as CYP3A4 substrates; however more work is needed in order to fully validate this approach. Due to the complexity of the analysis, we simplified several aspects that would have a clear impact on predicted $F_{rel}$. One of them was to assume a virtual reference human, thus eliminating the inter-individual variability on the physiological factors that influence drug absorption (Jamei et al., 2009a).

5. Conclusion

A factorial sensitivity analysis was performed for the investigation of the differences between immediate release and controlled release formulations on drug absorption, first pass metabolism and systemic exposure. This was complemented with a literature survey of the observed differences in oral bioavailability of CR formulations of CYP3A4 substrates. The use of a PBPK absorption model allowed the simultaneous consideration of both formulation and drug-specific properties. In general, a reduced absorption was observed when employing a controlled release formulation. The results matched previous observations made for colonic absorption (Tannergren et al., 2009). However, in some cases the reduction in $f_a$ was compensated by a reduction in intestinal metabolism, thus leading to a net increase in systemic exposure. This increase was both permeability and CYP3A4-affinity dependent. In addition, CR formulations of highly CYP3A4-cleared compounds were more likely to display higher relative bioavailability than the IR formulations. The simulations were in agreement with the observed clinical data for a number of CYP3A4 substrates. This study provided further support to the hypothesis that the observed higher relative bioavailability of CR formulations of highly cleared CYP3A4 could be due to differences in the intestinal first-pass metabolism. The outcome of this simulation study can be taken as a first step, as drug-specific simulations are required in order to fully support the PBPK approach for investigation of these metabolic and absorption differences. For P-gp substrates that were not subject to first-pass metabolism, no clear differences between the CR and IR formulation were observed. Finally, an interplay between CYP3A4 and P-gp was observed for IR formulations, however, more data is needed to investigate the mechanism of such phenomena.

Conflict of interest

The authors declare no conflict of interest. A.R.-H. is currently on a part-time secondment to Simcyp Ltd. (a Certara company) and holds shares in Certara. The Simcyp® simulator is freely available, following completion of the training workshop, to approved members of academic institutions and other non-for-profit organizations for research and teaching purposes.

Author contributions

A.O-M, A.S.D, L.A and A.R-H wrote the manuscript; A.O-M, A.S.D, L.A and A.R-H designed the study; Y.K and A.O.M performed literature search, A.O.M performed the simulations; Y.K, performed pilot study; A.O-M analysed the data.

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Appendix A. Supplementary material

The parameters employed for the simulations (Tables S1), the results from the literature search (Tables S2 and S3), the methodology employed for the calculations and the results for the scenarios not shown in this manuscript (Figs. S2–S6) and further discussion about the outcome of the simulations involving P-gp and the possible interplay with CYP3A4 can be found in the electronic Supplementary Material.

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