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Virtual bioequivalence for achlorhydric subjects: The use of PBPK modelling to assess the formulation-dependent effect of achlorhydria

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ABSTRACT

Majority of bioequivalence studies are conducted in healthy volunteers. It has been argued that bioequivalence may not necessarily hold true in relevant patient populations due to a variety of reasons which affect one formulation more than the other for instance in achlorhydric patients where elevated gastric pH may lead to differential effects on formulations which are pH-sensitive with respect to release or dissolution. We therefore examined achlorhydria-related disparity in bioequivalence of levothyroxine and nifedipine formulations using virtual bioequivalence within a physiologically-based pharmacokinetic (PBPK) modelling framework. The *in vitro* dissolution profiles at neutral pH were incorporated into PBPK models to mimic the achlorhydria with *in vitro–in vivo* relationship established using bio-relevant pH media. The PBPK models successfully reproduced the outcome of the bioequivalence studies in healthy volunteers under the normal conditions as well as under proton pump inhibitor-induced achlorhydria. The geometric mean test/reference ratios for C_{max} and AUC between levothyroxine tablet and capsule in patients receiving proton pump inhibitor were 1.21 (90%CI, 1.13–1.29) and 1.09 (90%CI, 1.02–1.17), respectively. Extension of the virtual bioequivalence study to Japanese elderly, who show high incidence of achlorhydria, indicated bio-inequivalence which C_{max} and AUC ratios between nifedipine control-released reference and test formulations were 3.08 (90%CI, 2.81–3.38) and 1.57 (90%CI, 1.43–1.74), respectively. Virtual bioequivalence studies through the PBPK models can highlight the need for conduct of specific studies in elderly Japanese populations where there are discrepancies in pH-sensitivity of dissolution between the test and reference formulations.

1. Introduction

A generic pharmaceutical product is marketed if it is therapeutically equivalent to the corresponding reference product containing the same active pharmaceutical ingredient (Davit et al., 2013). Therapeutic equivalence is assumed if the concentration-time profiles are similar. The same criteria is applied during the development of any propriety drug product when for variety of reasons the formulation is changed between early phase clinical studies and later studies prior to getting the drug into market. The pharmaceutical companies must demonstrate that the rate and extent of absorption from the new formulation is not significantly different from that of the reference formulation. Clinical studies to establish bioequivalence between two formulations are generally conducted in young healthy volunteers. The debate over the conduct of bioequivalence studies in patients as opposed to healthy volunteers is not a new one (Klintmalm, 2011; Morihara et al., 2001). However, the possibility to conduct "virtual bioequivalence" using *in silico* modelling of the target population is a new concept materialized with the advent of mechanistic models of oral drug absorption which combines *in vitro* information with the physiologically-based pharmacokinetic (PBPK) models to postulate *in vivo* consequences of any differences between formulations not only in healthy volunteers but in variety of other populations who are not typically assessed as part of the bioequivalence studies (Cristofoletti et al., 2017).

In the current study we have used achlorhydria as an example of attributes for gastro-intestinal tract that might have different incidence in the target population compared to the healthy volunteer populations which may cause disparities in the conclusions drawn regarding the bioequivalence in the two populations. Achlorhydria is defined as a state of the absence of hydrochloric acid in gastric juices. The prevalence of achlorhydria increases with age, and > 70% of Japanese elderly develop gastric hypoacidity (Morihara et al., 2001). Elevated gastric pH in achlorhydric elderly may affect bioequivalence between drug formulations where pH-sensitivity for *in vitro* dissolution differs.

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Administration of proton pump inhibitors induces gastric hypoacidity and also has the possibility to produce unacceptable results of bioequivalence between such drug formulations (Seng et al., 2015).

Several generic formulations of drugs such as levothyroxine and nifedipine show different pH-sensitivity of *in vitro* dissolution to the corresponding reference formulation (Garbacz et al., 2009; Pabla et al., 2009; Schug et al., 2002a, 2002b; Wonnemann et al., 2008). Levothyroxine, L-form of thyroid hormone thyroxine used for the treatment of hypothyroidism, is orally administered as tablets or a soft gelatin capsule where pH-sensitivity for *in vitro* dissolution differs between commercial products. Levothyroxine dissolves slowly from tablet at mild acidic and neutral pH compared to strong acidity, whereas soft gelatin capsule containing levothyroxine dissolved in glycerin shows a consistent dissolution profile without pH-dependency (Pabla et al., 2009). Once-daily tablet formulations of nifedipine, a calcium channel blocker used for the treatment of hypertension and angina, are marketed as control-released (CR) formulations where the release system differs such as oral osmotic push-pull system (OROS) and hydrophilic matrix tablets (Garbacz et al., 2009). An OROS tablet of nifedipine CR provides pH-independent dissolution profiles, while the corresponding hydrophilic matrix tablet has obvious pH-dependency of *in vitro* dissolution (Garbacz et al., 2009). Different pH-sensitivity of *in vitro* dissolution between these formulations raises issues concerning the possibility that bioequivalence cannot be necessarily assumed the same in healthy volunteer and achlorhydric patients population. The aim of study is to examine achlorhydria-related disparity in bioequivalence of levothyroxine and nifedipine CR formulations using virtual bioequivalence within PBPK modelling framework including *in vitro–in vivo* correlation (IVIVC) modelling.

2. Materials and methods

A workflow for virtual bioequivalence studies using the PBPK models that were applied to postulate *in vivo* consequences of any differences between formulations is outlined in Fig. 1.

2.1. Formulations

The levothyroxine sodium reference tablet and test capsule formulations used for virtual bioequivalence studies were Synthroid® (Abbott Laboratories, IL, USA) and Tirosint® (IBSA Institut Biochimique SA, Switzerland), respectively. The nifedipine CR reference and test formulations used for virtual bioequivalence studies were Adalat® OROS (Bayer AG, Germany) and Nifedipine Coral® (So.Se.PHARM S.r.l., Italy), respectively. *In vitro* dissolution profiles of the reference and test formulations for levothyroxine and nifedipine were obtained from the literature (Garbacz et al., 2009; Pabla et al., 2009). The dissolutions for levothyroxine formulations were carried out in dissolution medias containing 0.05% sodium lauryl sulfate, which were 0.1 N hydrochloric acid representing pH 1.2 and 0.05 M ammonium acetate buffers by adjusting the pH with acetic acid or ammonium hydroxide to 5.0, 6.0, or 7.0 (Pabla et al., 2009). The dissolutions for nifedipine CR formulations were carried out in USP simulated gastric fluid without enzymes pH 1.2 with 1% SDS, USP acetate buffer pH 4.5 with 1% SDS, and USP buffer solution for nifedipine extend release tablets pH 6.8 (Garbacz et al., 2009). These dissolution profiles were digitized using GetData Graph Digitizer version 2.26 (Fig. 2). Plasma levothyroxine concentration profiles with or without intravenous administration of esomeprazole and plasma nifedipine concentration profiles under fasted and fed state were also obtained from the literature and digitized (Colucci et al., 2011; Schug et al., 2002b; Seng et al., 2015).

2.2. PBPK model development

PBPK modelling and simulation was employed using the Simcyp® Simulator (V16.1; Certara, Sheffield, UK). PBPK model was developed

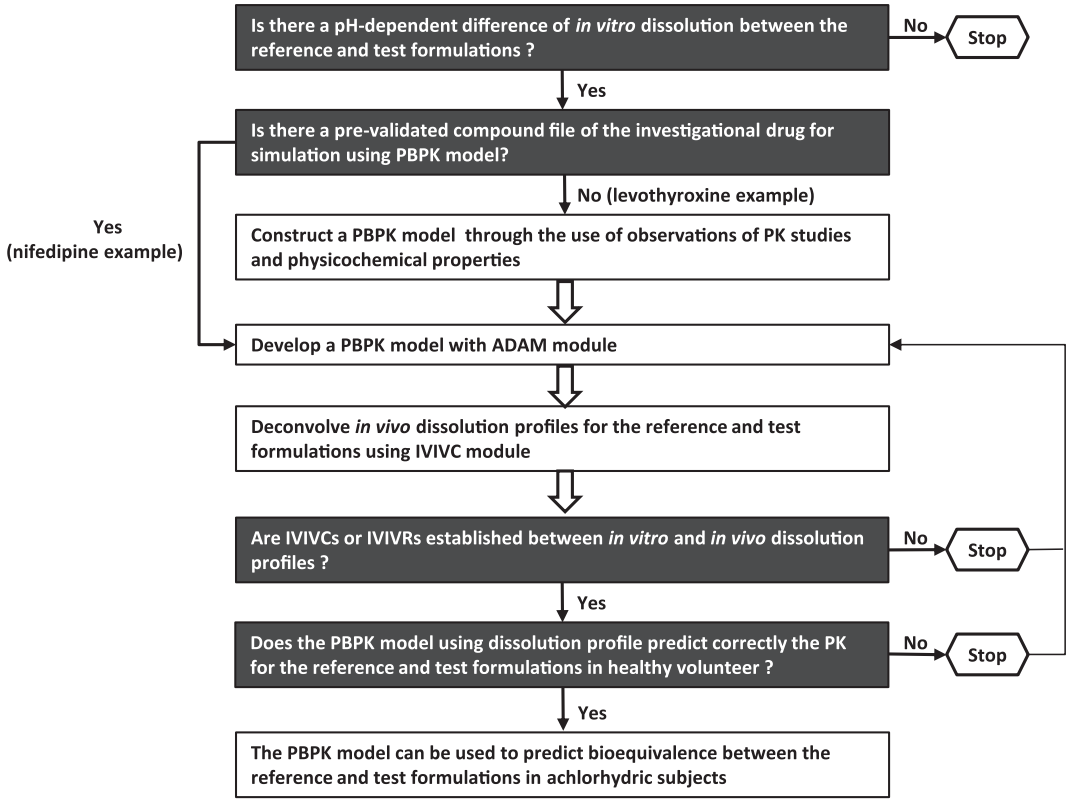

Fig. 1. Applied workflow for virtual bioequivalence studies using the physiologically-based pharmacokinetic (PBPK) models to postulate *in vivo* consequences of any differences between formulations. PK, pharmacokinetic; ADAM, Advanced Dissolution, Absorption and Metabolism; IVIVC, *in vitro–in vivo* correlation; IVIVR, *in vitro–in vivo* relationship.