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# Pharmacokinetic analysis of modified-release metoprolol formulations: An interspecies comparison

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ABSTRACT

In the current study, we investigated the metoprolol absorption kinetics of an in-house produced oral sustained-release formulation, matrices manufactured via prilling, and two commercially available formulations, ZOK-ZID® (reservoir) and Slow-Lopresor® (matrix) in both New Zealand White rabbits and Beagle dogs, using a population pharmacokinetic analysis approach.

The aim of this study was to compare the in vivo pharmacokinetic (PK) profiles of different formulations based on metoprolol, a selective adrenergic $\beta_1$-receptor antagonist, in dogs and rabbits and to contrast the observed differences. To that end, metoprolol (50 to 200 mg) was administered to 6 Beagle dogs and 6 New Zealand White rabbits as a single intravenous (IV) bolus injection and to 8 dogs and 6 rabbits as an oral modified release formulation. To derive pharmacokinetic parameters from the data, a non-linear mixed-effects model was developed using NONMEM® where the contribution of observations below the limit of detection (BDL, below detection limit) to the parameter estimates was taken into account in the parameter estimation procedure.

In both species and for the three modified release formulations, different absorption models were tested to describe the PK of metoprolol following oral dosing. In Beagle dogs, plasma concentration-time profiles were best described using a sequential zero- and first-order absorption model. In rabbits though, the absorption phase was best described using a first-order process only.

In both species, the reservoir formulation ZOK-ZID® was behaving quite similarly. In contrast, the absorption properties of both matrix formulations were rather different between species. This study indicates that the PK of the reservoir formulation is similar in both species, even after accounting for the almost completely missed absorption phase in rabbits. The insights gained further illustrate that rabbits are not very well suited to study the PK of the current matrix formulations in view of their less optimal prolonged release characteristics and the resulting fast decline in metoprolol plasma levels.



## 1. Introduction

The aim of the present study was to compare the absorption kinetics of metoprolol from three types of modified-release dosage forms, both in the frequently used preclinical animal models Beagle dogs and New Zealand White rabbits, and to evaluate the observed differences. Metoprolol is a $\beta_1$-selective adrenergic blocking agent, commonly used in the treatment of hypertension, angina pectoris and heart failure. Being a Class I compound, according to the Biopharmaceutics Classification System (BCS), it possesses both a high solubility and permeability. However, as metoprolol is characterized by a short half-life (3-4 h) caused by extensive hepatic first-pass metabolism, frequent dosing during the day is required (Åblad et al., 1975; Regårdh et al., 2015). Hence, the drug is a suitable candidate for incorporation into a controlled release dosage form that delivers the drug over an extended period of time thereby significantly decreasing the frequency of dosing.

Metoprolol's bioavailability of an in-house developed multiparticulate sustained-release matrix system by means of prilling was compared with two commercially available modified-release formulations: Slow-Lopresor® (Daiichi Sankyo Belgium S.A., Louvain-la-Neuve, Belgium) and ZOK-ZID® (Pfizer S.A., Brussels, Belgium). While Slow-Lopresor® represents a controlled release matrix tablet, ZOK-ZID® is a tablet which immediately disintegrates into reservoir coated pellets.

Here, we present a model-based analysis to compare metoprolol pharmacokinetics between ZOK-ZID®, Slow-Lopresor® and the in-house produced prills in the selected preclinical species.

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## 2. Materials and Methods

### 2.1. Materials

Metoprolol tartrate was purchased from Esteve Quimica (Barcelona, Spain), while behenic acid (Radiacid 0560) was purchased from Oleon (Ertvelde, Belgium). Polyethylene glycol (PEG) 4000 was obtained from Fagron (Waregem, Belgium). All other chemicals were of analytical grade.

### 2.2. Prilling

An in-house developed multiparticulate sustained-release matrix system was prepared by means of prilling. This technique basically consists of converting a liquid melt into droplets that are subsequently cooled below their solidification temperature (Rahmanian et al., 2013). The process initially involves the solubilization or dispersion of a drug into a molten lipid base before extrusion through calibrated nozzles. The break-up of the liquid jet allows perfect calibration of the droplets and finally results in the production of narrow-sized spherically shaped particles, called prills (Pivette et al., 2009, 2012). Due to the hydrophobic properties of the lipids, the process is able to produce diffusion-controlled matrix systems.

Prilling was performed using the PrillDrop® device developed by Peira (Turnhout, Belgium). Behenic acid and PEG 4000 were simultaneously molten and the drug was added under stirring. The mixture was heated to 100 °C before droplet formation was started. By applying air pressure, the mixture was fed towards the thermostated nozzle (90 °C) consisting of a valve and a needle (inner diameter: 0.33 mm). Using a drop time of 0.04 s (i.e. period during which the valve is open) and an air pressure of 0.5 bar, droplets were produced at the needle. Finally, these droplets were quench cooled in liquid nitrogen yielding solid spherical particles. Thermogravimetric analysis indicated that metoprolol tartrate, behenic acid and PEG 4000 were stable at the process temperature (data not shown). The prills showed a mean particle size of 2.4 mm with narrow particle size distribution. Furthermore, the prills exhibited perfect sphericity with a mean aspect ratio of 1.1.

### 2.3. In Vitro and In Vivo Study

#### 2.3.1. In Vitro Dissolution Profile Study

In vitro drug release was determined using the USP dissolution apparatus 1 (baskets). The equipment consisted of a VK 7010 system coupled with a VK 8000 automatic sampling station (Vankel, New Jersey, USA). In case of the prills, an amount of prills corresponding to 30 mg metoprolol tartrate was exposed to the dissolution medium, whereas 1 tablet was tested in case of Slow-Lopresor® (200 mg metoprolol tartrate) and ZOK-ZID® (95 mg metoprolol succinate). The dissolution medium consisted of 900 mL of demineralized water. Basket rotational speed was set at 100 rpm and the temperature of the dissolution medium was maintained at 37 ± 0.5 °C. Samples of 5 mL were withdrawn after 0.5, 1, 2, 4, 6, 8, 12, 16, 20 and 24 h and analyzed spectrophotometrically at 222 nm using a double beam spectrophotometer (UV-1650PC, Shimadzu, Antwerp, Belgium). Metoprolol concentrations were calculated from a calibration curve between 0 and 33 μg/mL.

#### 2.3.2. In Vivo Animal Study

All procedures were performed in accordance with the guidelines and after approval by the local Ethics Committee. Each time, 8 dogs and 6 rabbits were orally dosed with (i) the prills containing 10% metoprolol tartrate, 5% PEG 4000 and 85% behenic acid (filled in hard-gelatin capsules), (ii) the commercial reservoir formulation, ZOK-ZID®, consisting of tablets containing 95 mg metoprolol succinate (equivalent to 100 mg metoprolol tartrate) and (iii) the commercial matrix formulation, Slow-Lopresor®, containing 200 mg metoprolol tartrate. The intravenous (IV) bolus injection was administered to 6 dogs and 6 rabbits. For the oral formulations, 200 mg metoprolol tartrate was administered to the dogs, while 100 mg metoprolol tartrate was administered to the rabbits. Beagle dogs were treated with two tablets of ZOK-ZID® and rabbits received one tablet. Slow-Lopresor® was dosed as one tablet to Beagle dogs and rabbits received half a tablet. In case of the intravenous injection, an isotonic solution was made based on metoprolol tartrate. The IV dose administered was 100 mg and 50 mg for the dogs and rabbits, respectively.

The formulations were administered in a cross-over fashion with a wash-out period of at least 7 days. All animals were fasted from 12 h prior till 12 h after dose administration, although water was available ad libitum. Before dose administration, a blank blood sample was collected. The oral formulations were administered with 20 mL water. Blood samples were collected in dry heparinized tubes at predetermined time points after drug administration, centrifuged at 1500 × $g$ for 5 min and resulting plasma was stored at −20 °C until analysis.

### 2.4. HPLC Analysis

A validated HPLC method with fluorescence detection was used for the determination of metoprolol in plasma. We refer to the paper written by Vervaeck et al. (2013) for more details.

### 2.5. Population PK Analysis Methods

Due to the significant number of samples below the quantification limit (BQL) and the fact that the extrapolated area under the curve (AUC) is higher than 20% for all formulations, except for Slow-Lopresor® in dogs (10.36%), the data were analyzed using population pharmacokinetic analysis with implementation of the M3 method (Ahn et al., 2008; Jusko, 2012; Keizer et al., 2015), instead of non-compartmental analysis to avoid biased PK parameters.

A total of 258 and 205 ln-transformed metoprolol observations sampled from 30 Beagle dogs and 24 rabbits were available for population PK analysis. Population PK analysis was performed by means of nonlinear mixed-effects modeling using NONMEM® (version 7.3.0, ICON, Hanover, MD, USA). All NONMEM runs were executed using Pearl-speaks-NONMEM (PsN) 4.2.0 (Beal et al., 2011; Lindbom et al., 2005). The statistical package R (version 3.1.2, R Development Core Team, 2011) was used during model development for a graphical assessment of the goodness-of-fit (GOF) of the different tested models.

In the first stage of model development, one- and two-compartment models with linear elimination from the central compartment were fitted to the IV data alone using the first-order conditional estimation (FOCE) method. Thereafter, oral data were combined with IV data and the absorption part of the model was optimized. During model development, a first order absorption process besides models assuming parallel or sequential zero- and first-order absorption pathways were tested.

Observations between the limit of detection (10.1 ng/mL) and the limit of quantification (30.6 ng/mL) were taken into account during the analysis, whereas BDL data were analyzed using the M3 method (Ahn et al., 2008; Jusko, 2012; Keizer et al., 2015). The percentages of BQL and BDL data were 9.5% and 6.2% in Beagles and 16.5% and 6% in rabbits, respectively, indicating that the BQL data need to be considered during the analysis in order to avoid bias in parameter estimates. The M3-method was suggested by Beal to handle data below the limit of quantification and is based on maximization of the likelihood for all the data. The M3 method includes simultaneous modeling of continuous and categorical data by treating the BQL observations as censored categorical data. We applied this method on our retained BDL observations in the dataset, using the indicator variable F_FLAG.

Population PK parameters including their inter-individual variability (IIV), and the residual unexplained variability (RUV) were estimated using the LAPLACIAN estimation method. Inter-individual variability around the typical PK parameters was estimated using an exponential