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# Pharmacometric characterization of entero-hepatic circulation processes of orally administered formulations of amiodarone under complex binding kinetics

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95%ci, confidence intervals 95%
Am, amiodarone
Her, entero-hepatic reabsorption
Gof, goodness of fit
Iv, intravenous
Iiv, inter-individual variability
OFV, objective function value
OR, oral
pc-VPC, prediction-corrected visual predictive checks
PK, pharmacokinetics
RUV, residual unexplained variability

ABSTRACT

*Aims:* The aims of this work are (i) to characterize the absorption properties of orally administered formulations at different dose levels, and (ii) to evaluate the impact of entero-hepatic circulation on the time-course of amiodarone (AM) in rats in order to optimize the development of new oral (OR) formulations.
*Methods:* Intravenous (IV) formulation consisted on a solution of a commercial injectable of AM chlorhydrate. OR formulations included the IV commercial formulation (Trangorex®) (Solution I), an aqueous supramicellar solution of AM chlorhydrate with Polysorbate at 5% (Solution II) and a suspension from Trangorex® tablets (Tablet). Data from 96 male Wistar rats, including 985 AM observations, were analyzed using NONMEM v7.4.
*Results:* The population pharmacokinetic (PK) model assumes linear absorption processes, showing $k_a$ of AM from Solution II (Polysorbate 80, 5%) and Solution I increased by 2.5- and 1.62-fold compared to Tablet formulation. OR bioavailability of AM from Tablet, Solution I and Solution II was 37%, 40%, and 50%, respectively. The structural model of AM disposition was adapted from a previously population PK model and expanded by incorporating entero-hepatic reabsorption (EHR) processes, which estimated a 12.3% biliary excretion of AM and complete re-absorption from lumen.
*Conclusions:* The current population PK model of AM demonstrated the absorption rate enhancement when AM is formulated with supramicellar concentrations of Polysorbate 80. The study design allowed to characterize the EHR of AM and its contribution in the overall AM disposition.

## 1. Introduction

Amiodarone (AM), an iodine-rich benzofuran derivative, is a class III antiarrhythmic medication, which is indicated for the treatment of life-threatening ventricular arrhythmias, supraventricular arrhythmias and atrial fibrillation. Despite having demonstrated a high effectiveness as antiarrhythmic medication in clinical practice, long-term therapy can result in a wide variety of side effects affecting several organ systems, some of which can be life threatening (Cahoon et al., 2007; Mujović et al., 2020). Commercially available AM presentations include intravenous (IV) and oral (OR) formulations, being the latter indicated in patients with mild and moderate heart disease, whereas IV route of administration is preferred in hemodynamically destabilizing ventricular tachycardia or ventricular fibrillation or when patients are unable to

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**Table 1**
Summary of study design characteristics.

| Route of administration | Schedule | Dose (mg) | Formulation | Sample | N° Animals | N° Observations |
|---|---|---|---|---|---|---|
| IV | SD | 12.5 | Solution I | Blood | 16 | 231 |
| | | | Solution I | Blood, Bile$^{NC}$ | 6 | 84 |
| | | | Solution I | Blood, Bile$^{CC}$ | 6 | 82 |
| OR | SD | 10 | Solution II | Blood | 8 | 63 |
| OR | SD | 25 | Tablet | Blood | 8 | 68 |
| OR | SD | 25 | Solution I | Blood | 8 | 59 |
| IV+IV | MD | 12.5 + 12.5 ($t$ = 24 h) | Solution *I*+ Solution I | Blood | 8 | 93 |
| IV+OR | MD | 12.5 + 25 ($t$ = 24 h) | Solution *I* +Tablet | Blood | 8 | 102 |
| IV+OR | MD | 12.5 + 25 ($t$ = 24 h) | Solution *I* +Solution I | Blood | 8 | 103 |
| IV+OR | MD | 12.5 + 10 ($t$ = 24 h) | Solution *I* +Solution II | Blood | 8 | 100 |

Abbreviations: IV: intravenous; OR: oral; SD: single dose; MD: multiple doses, n: number.

take oral medications (Mujović et al., 2020). AM is given as a monotherapy or in combination with other drugs (e.g. β-adrenergic antagonists, calcium channel blocking agents or digoxin), showing its effectiveness in several clinical trials (Andrade et al., 2010; Cappelletto et al., 2021; Hamer et al., 1989; Kim et al., 2014; Lupercio et al., 2018; Mitchell et al., 2005; Mooss et al., 1990; Somberg and Molnar, 2016; Somberg et al., 2004). In addition, AM is one of the most effective pharmacological agents with extensive off-label use for the treatment of supraventricular arrhythmia in children (Etheridge et al., 2001; Moak, 2000; Saul et al., 2005). Despite of its outstanding pharmacological properties, the slow onset of its antiarrhythmic action, the presence of multiple drug-drug interactions and the several safety concerns, including ophthalmological, pulmonary, and neurological toxicity after its chronic administration has limited its use in clinical practice (Mujović et al., 2020).

AM according to the Biopharmaceutics Classification System (Amidon et al., 1995) is a class III drug, with low solubility (0.35 mg/mL) (Wang et al., 2017) and high permeability drug due to its high lipophilicity, which explains its large distribution into highly perfused and lipophilic tissues. Approved dosing schedules for maintenance regimens ranged from 200 to 400 mg/day (Siddoway, 2003). Slow and variable AM absorption has been reported, reaching a maximal plasma concentration between 3 and 7 h after oral administration and a moderate bioavailability (35–65%). High protein binding (>96%) has been reported (Lalloz et al., 1984; Veronese et al., 1988) predominately to albumin, but also to β-lipoprotein, and large accumulation of AM in liver, lung, adipose tissue, skeletal muscles and skin has been reported (Kodama et al., 1997; Plomp et al., 1987; Singh, 2006; Zimetbaum, 2012). Recently Hashimoto et al. (2021) found serum amiodarone concentrations increased in patients with hypertriglyceridemia state since as the concentration of LDL/VLDL increases, the fraction of drug bound increases restricting its distribution to other organs/tissues and hepatic metabolism of amiodarone. AM is metabolized primarily to desethylamiodarone through the cytochrome P450 enzyme CYP3A4, and by CYP2C8. The major route of elimination is hepatic excretion into bile with some degree of entero-hepatic recirculation and the renal excretion for AM is negligible in humans (Haffajee, 1987; Pollak et al., 2000; Somani, 1989). A therapeutic range of AM from 1.0 to 2.5 mg/L has been suggested (Haffajee et al., 1983; Rotmensch et al., 1984), and adverse reactions have been reported at amiodarone concentrations above 2.6 mg/L (Falik et al., 1987; Greenberg et al., 1987; Rotmensch et al., 1984). Complexity in AM pharmacokinetics properties, including the reduced and variable oral absorption, associated with the high inter-individual variability (IIV) in plasma levels, and its narrow therapeutic index due to the high risk of drug toxicity has limited the therapeutic usefulness of AM for its chronic administration. New OR formulations have been developed recently to improve the clinical use of AM focusing on the improvement of its water-solubility and bioavailability, demonstrating the need to improve the technological properties of OR formulations of AM for an optimal therapeutic use (Beig et al., 2015; Creţeanu et al., 2015; Elgart et al., 2013; Patel et al., 2015a; Wang et al., 2017).

Preclinical characterization of complex pharmacokinetic properties through model-informed approaches has been widely considered during the drug development process and has demonstrated its utility for an optimal selection of dosing regimens in first-time-in-humans studies (Biliouris et al., 2018; Choi et al., 2019; Dong et al., 2011; Kang et al., 2021; Kwak et al., 2021; Li et al., 2019; Luu et al., 2012; Nirogi et al., 2020; Song et al., 2020; Zou et al., 2012). The advantage of this strategy becomes even more evident when non-linear kinetic processes come into play, since the classical approaches for data analysis are unable to accurately determine the magnitude of the effects together. In this regard, non-linear mixed effects modeling allows to quantitatively characterize the central tendency of the experimental data and the different sources of variability in order to accurately describe the observed behavior (Bonate, 1999). Therefore, the aims of this pre-clinical study are (i) to characterize the absorption properties of different orally administered formulations and at different dose levels, and (ii) to evaluate the impact of entero-hepatic circulation on the time-course of AM in rats in order to optimize the development of new OR formulations of AM.

**Table 2**
Composition of oral formulations of Amiodarone administered.

| Formulations | Composition | |
|---|---|---|
| Solution I | Amiodarone chlorhydrate | 0.150 g |
| | Polysorbate 80 | 0.300 g |
| | Benzyl alcohol | 0.060 g |
| | Bidistilled water q.s. | 3 mL |
| Tablet | Amiodarone chlorhydrate | 0.200 g |
| | Lactose | 0.071 g |
| | Cornstarch | 0.066 g |
| | Polividone | 0.006 g |
| | Colloidal silica | 0.0024 g |
| | Magnesium stearate | 0.0046 g |
| Solution II | Amiodarone chlorhydrate Polysorbate 80 | 5 mg/mL<br>5% |

## 2. Materials and methods

### 2.1. Study design

All pharmacokinetic studies reported here adhere to the Principles of Laboratory Animal Care and were approved by the Research Committee of Animal Use from the Faculty of Pharmacy from University of Valencia (Spain). Data were obtained from the doctoral theses presented by Pascual-Costa (1994) and Chicano-Piá (1998). The experimental dataset consisted of 96 male Wistar rats of 20-weeks, 250–320 g body weight, including 985 AM observations in plasma ($n$ = 901) and bile ($n$ = 84). Wistar rats were housed under pathogen-free conditions, on a 12 h light/dark cycle, with controlled temperature (22–24 °C) and humidity (25%). Food and water were given ad libitum. IV and OR routes of administration of AM at different dose levels were evaluated, including

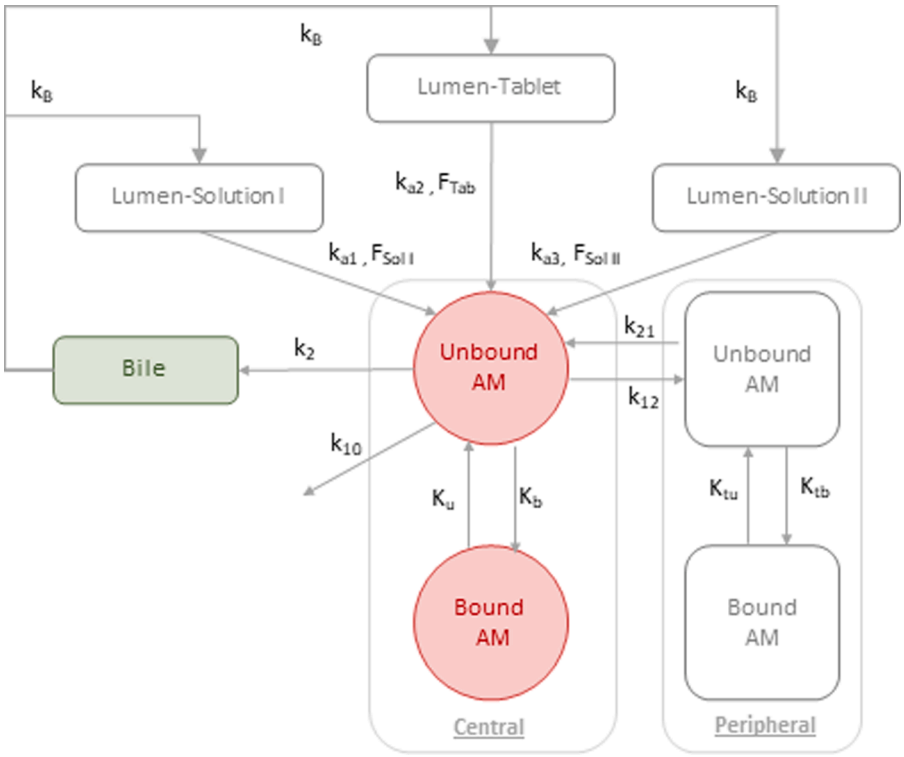


**Fig. 1.** Schematic representation of the final PK model developed.
$k_B$: first-order rate constant from bile, $k_{a1}$: first-order absorption rate constant of Solution I formulation, $F_{Sol\ I}$: oral bioavailability of Solution I formulation, $k_{a2}$: first-order absorption rate constant of Tablet formulation, $F_{Tab}$: oral bioavailability of Tablet formulation, $k_{a3}$: first-order absorption rate constant of Solution II formulation, $F_{Sol\ II}$: oral bioavailability of Solution II formulation, $k_{10}$: first-order elimination rate constant, $k_2$: first-order distribution constant, $K_u$: rate constant of unbinding in central compartment, $K_b$: rate constant of binding in central compartment, $K_{tu}$: rate constant of unbinding in peripheral compartment, $K_{tb}$: rate constant of binding in peripheral compartment, $k_{21}$: first-order distribution constant from central to peripheral compartment, $k_{12}$: first-order rate constant from peripheral to central compartment.

single and multiple dosing regimens. Different sampling strategies were considered based on the route of administration and schedule, but all samples were collected to ensure the characterization of the PK profile of each animal. Table 1 summarizes the characteristics of the study, including, dose of AM administered for each administration route and number of animals enrolled and samples available in each group.

IV formulation was the commercial injectable of AM chlorhydrate (Trangorex®, 50 mg/ml). Three OR formulations of AM were evaluated, including the IV injectable (Trangorex®, Solution I, 50 mg/ml), a suspension from Trangorex® tablets (Tablet, 200 mg) and a solution with 5% Polysorbate 80 (Solution II, 5 mg/ml). The composition of the formulations is detailed in Table 2.

### 2.2. Blood sampling and analytical methods

Twenty-four hours before the administration of AM, the jugular vein, and portions of the bile duct and the small intestine were channeled in the different groups of rats. Prior to the surgical intervention, a dose of 2.7 ml/kg of anesthesia solution was administered by an intraperitoneal injection. The anesthesia was prepared by mixing solutions of 5 mg/ml diazepam, 50 mg/ml ketamine and 1 mg/ml atropine. After surgery and until drug administration, animals were kept fasted overnight with water freely available.

Drug administration of the three OR formulations was performed through a gastric tube. Blood samples (0.5 ml) were withdrawn into heparinized syringes from the jugular vein cannula, then centrifuged at 3000 r.p.m. for 5 min and stored at −20 °C. Bile samples were collected from two groups of rats with continuous enterohepatic cycle (CC group) and non- continuous enterohepatic cycle (NC group). In the CC group, the enterohepatic cycle was maintained, and the flowing bile was collected for 5 min before and 5 min after the administration of AM, disconnecting the bridging tubes of the bile duct and small intestine. In the NC group, the enterohepatic cycle was interrupted as soon as AM was administered, disconnecting the bridging tube from the bile duct catheter. Bile samples were stored at 4–8 °C (Chicano-Piá, 1998; Pascual-Costa, 1994).

The quantification of AM in plasma and bile samples was performed through high performance liquid chromatography with spectrophotometric detection under ultraviolet light at a wavelength of 242 nm. The chromatographic method was validated following the recommendations of the International Conference on harmonisation (ICH, 1995) in terms of linearity, precision (intra- and interday), accuracy, limit of detection and quantification, specificity, interval and robustness. The limit of quantification was 0.1 μg/ml.

### 2.3. Pharmacokinetic model

The modeling strategy used a previously developed population PK model (Campos Moreno et al., 2007) in rats after IV administration, which contained a two-compartment model with saturable dynamic plasma protein and linear tissular depot binding in the peripheral compartment. Equal PK parametrization of the disposition of AM was assumed as described by Campos Moreno et al. (2007). Then, the model (Fig. 1) was adapted to describe the absorption kinetics of AM from the three OR formulations administered to the rats by assuming linear absorption kinetics. Non-linear absorption kinetics, absorption latency and complex absorption processes (parallel absorption, precipitation, transit compartments, etc.) were also evaluated. EHR of AM was modelled through linear kinetic processes of AM transition into and out of the bile compartment.

### 2.4. Data analysis

Plasma observations were logarithmically transformed. All data analyses were performed based on the population approach with the software NONMEM® (v7.4, ICON plc Development Solutions, Hanover, MD, USA). The population PK parameters were estimated using the Stochastic Approximation of the Expectation Maximization and the Importance Sampling Estimation method.

IIV associated to the PK model parameters was modeled exponentially preventing negative values for the individual estimates, and residual unexplained variability (RUV) was described with an additive

model on the logarithmic scale. The significance of the non-diagonal elements of the Ω variance-covariance matrix and subject specific RUV were also evaluated.

#### 2.4.1. Model selection

Model selection was based on physiological and pharmacological rationale with the principle of parsimony (Wade et al., 1994). The minimum value of the objective function value (OFV) provided by NONMEM® and approximately equal to −2xlog (likelihood) (−2LL) was used together with the visual inspection of the goodness of fit (GOF) plots to perform model selection. A decrease in 6.63 points in −2LL value between two nested models differing in one parameter was considered significant at the 1% level.

#### 2.4.2. Model evaluation

Model evaluation of the selected models was performed through prediction-corrected visual predictive checks (pc-VPC). Briefly, one thousand simulated datasets were simulated; the 2.5th, 50th, and 97.5th percentiles for every simulated study and sampling time-period were calculated. Then, the 95% prediction intervals of the percentiles were calculated and displayed graphically together with corresponding percentiles computed from raw data. In addition, the condition number, computed as the ratio of the largest eigenvalue to the smallest eigenvalue of the variance-covariance matrix, was calculated. A condition number less than 400 was targeted as it indicates good stability in the parameter estimates (Bonate, 1999). Precision of model parameter estimates, defined as the relative standard error (RSE), were calculated from the variance-covariance matrix (when possible) and from the analysis of one thousand simulated bootstrap datasets.

For graphical and statistical analysis, the R software (http://cran.r-project.org, version 4.0.3) was used. Pc-VPC and bootstrap analysis were performed using PsN.

## 3. Results

### 3.1. Pharmacokinetic model

The absorption process after the OR administration of three formulations of AM (Solution I, Tablet and Solution II) were described through a linear process using different first order absorption rate constants for each formulation ($k_{a1-3}$). The results suggest a major improvement in $k_a$ when AM was administered as solution in the presence of 5% of Polysorbate 80 (Solution II: 250% increase) and 10% of Polysorbate 80 (Solution I: 62% increase) compared to Tablet formulation. Alternative mechanisms were also evaluated (i.e. zero-order absorption, non-linear kinetics, sequential/parallel first-and zero-order processes, transit compartment) but resulted in worse model performance ($p > 0.01$). AM showed a moderate OR bioavailability, which was parametrized independently for each formulation. Tablet showed less OR bioavailability (37%), compared to Solution I (40%) and Solution II (50%). These results reinforce the idea that OR bioavailability of AM could be enhanced by the presence of supramicellar concentration of surfactants that help to increase the AM solubility and dissolution process in the intestinal lumen (Elgart et al., 2013; Wang et al., 2017).

The structural model of AM disposition was adapted from a previous publication (Campos Moreno et al., 2007) in order to characterize PK longitudinal data of AM after IV and OR administration for new dose levels and dosing regimens (Table 1), which included a saturable and non-instantaneous plasma protein binding of AM ($B_{max}$, $C_{50}$ and $K_u$) and linear tissue binding in the peripheral compartment ($K_{tb}$ and $K_{tu}$). The first order binding rate constant ($K_b$) was derived as $K_u/C_{50}$ and the binding saturation in plasma was modeled considering the available binding capacity. Peripheral distribution of AM occurred only between free fractions of the central and peripheral compartment through linear kinetics ($k_{12}$, $k_{21}$), suggesting a large distribution of AM into the peripheral compartment due to its high lipophilicity. The total protein binding in plasma was characterized through the $B_{max}$ parameter, which was assumed as 5.05 mg based on the previous population PK model developed with IV data (Campos Moreno et al., 2007). A more detailed description of the equations governing the PK of AM have been previously published (Campos Moreno et al., 2007). The PK disposition model of AM was expanded by incorporating an EHR process of AM, which assumed a linear distribution process of AM from the unbound central compartment into the bile compartment and its transit into the lumen through a first-order rate constant ($k_B$=12.9 $h^{-1}$). The absence of a gallbladder in rats leads to a constant distribution of the bile content into the lumen, preventing the implementation of more complex EHR models

**Table 3**
Final population pharmacokinetic parameters after sub-cutaneous administration of reserpine in rats.

| | Population PK model estimates | | Bootstrap results | |
|---|---|---|---|---|
| ***Fixed-effect*** | Value | Shrinkage (%) | Median | 95%CI |
| $k_{a1}$ ($h^{-1}$) | 1.33 × $10^{-1}$ | | 1.34 × $10^{-1}$ | [1.16–1.49] x$10^{-1}$ |
| $k_{a2}$ ($h^{-1}$) | 8.20 × $10^{-2}$ | | 8.24 × $10^{-2}$ | [7.69–8.87] x$10^{-2}$ |
| $k_{a3}$ ($h^{-1}$) | 2.05 × $10^{-1}$ | | 2.02 × $10^{-1}$ | [1.67–2.51] x$10^{-1}$ |
| $F_{Sol\ I}$ (%) | 4.02 × $10^{1}$ | | 4.03 × $10^{1}$ | [3.71–4.26] x$10^{1}$ |
| $F_{Tab}$ (%) | 3.71 × $10^{1}$ | | 3.75 × $10^{1}$ | [2.79–4.12] x$10^{1}$ |
| $F_{Sol\ II}$ (%) | 5.05 × $10^{1}$ | | 5.02 × $10^{1}$ | [4.21–6.19] x$10^{1}$ |
| $k_{12}$ ($h^{-1}$) | 7.17 × $10^{1}$ FIX | | 7.17 × $10^{1}$ FIX | |
| $k_{21}$ ($h^{-1}$) | 4.64 × $10^{-1}$ FIX | | 4.64 × $10^{-1}$ FIX | |
| $V_2$ (L) | 1.44 × $10^{-2}$ FIX | | 1.44 × $10^{-2}$ FIX | |
| $B_{max}$ (mg) | 5.05 × $10^{\circ}$ FIX | | 5.05 × $10^{\circ}$ FIX | |
| $C_{50}$ (mg/L) | 1.49 × $10^{1}$ FIX | | 1.49 × $10^{1}$ FIX | |
| $K_u$ ($h^{-1}$) | 5.42 × $10^{\circ}$ FIX | | 5.42 × $10^{\circ}$ FIX | |
| $K_{tb}$ ($h^{-1}$) | 1.63 × $10^{-1}$ FIX | | 1.63 × $10^{-1}$ FIX | |
| $K_{tu}$ ($h^{-1}$) | 9.87 × $10^{-2}$ FIX | | 9.87 × $10^{-2}$ FIX | |
| $k_B$ ($h^{-1}$) | 1.29 × $10^{1}$ | | 1.28 × $10^{1}$ | [1.07–1.42] x$10^{1}$ |
| $k_{10}$ ($h^{-1}$) | 2.98 × $10^{1}$ FIX | | 2.98 × $10^{1}$ FIX | |
| ***Inter-individual variability*** | | | | |
| $k_{a1}$ (%) | 39 | 16 | 41 | [31–56] |
| $k_{a2-3}$ (%) | 34 | 21 | 35 | [27–41] |
| $k_{12}$ (%) | 24 | 32 | 27 | [19–33] |
| $V_2$ (%) | 46 | 26 | 42 | [31–58] |
| $K_u$ (%) | 13 | 38 | 12 | [9–15] |
| ***Residual unexplained variability*** | | | | |
| Plasma (%) | 46 | 7 | 45 | [42–49] |

$k_{a1}$: first-order absorption rate constant of Solution I formulation, $F_{Sol\ I}$: oral bioavailability of Solution I formulation, $k_{a2}$: first-order absorption rate constant of Tablet formulation, $F_{Tab}$: oral bioavailability of Tablet formulation, $k_{a3}$: first-order absorption rate constant of Solution II formulation, $F_{Sol\ II}$: oral bioavailability of Solution II formulation, $k_{12}$: first-order rate constant from peripheral to central compartment, $k_{21}$: first-order distribution constant from central to peripheral compartment, $V_2$: apparent central volume of the central compartment, $B_{max}$: maximal binding capacity, $C_{50}$: AM unbounded plasma concentration that produces a $B_{max}/2$, $K_u$: rate constant of unbinding in central compartment, $K_{tu}$: rate constant of unbinding in peripheral compartment, $K_{tb}$: rate constant of binding in peripheral compartment, $k_B$: first-order rate constant from bile, $k_{10}$: first-order elimination rate constant.

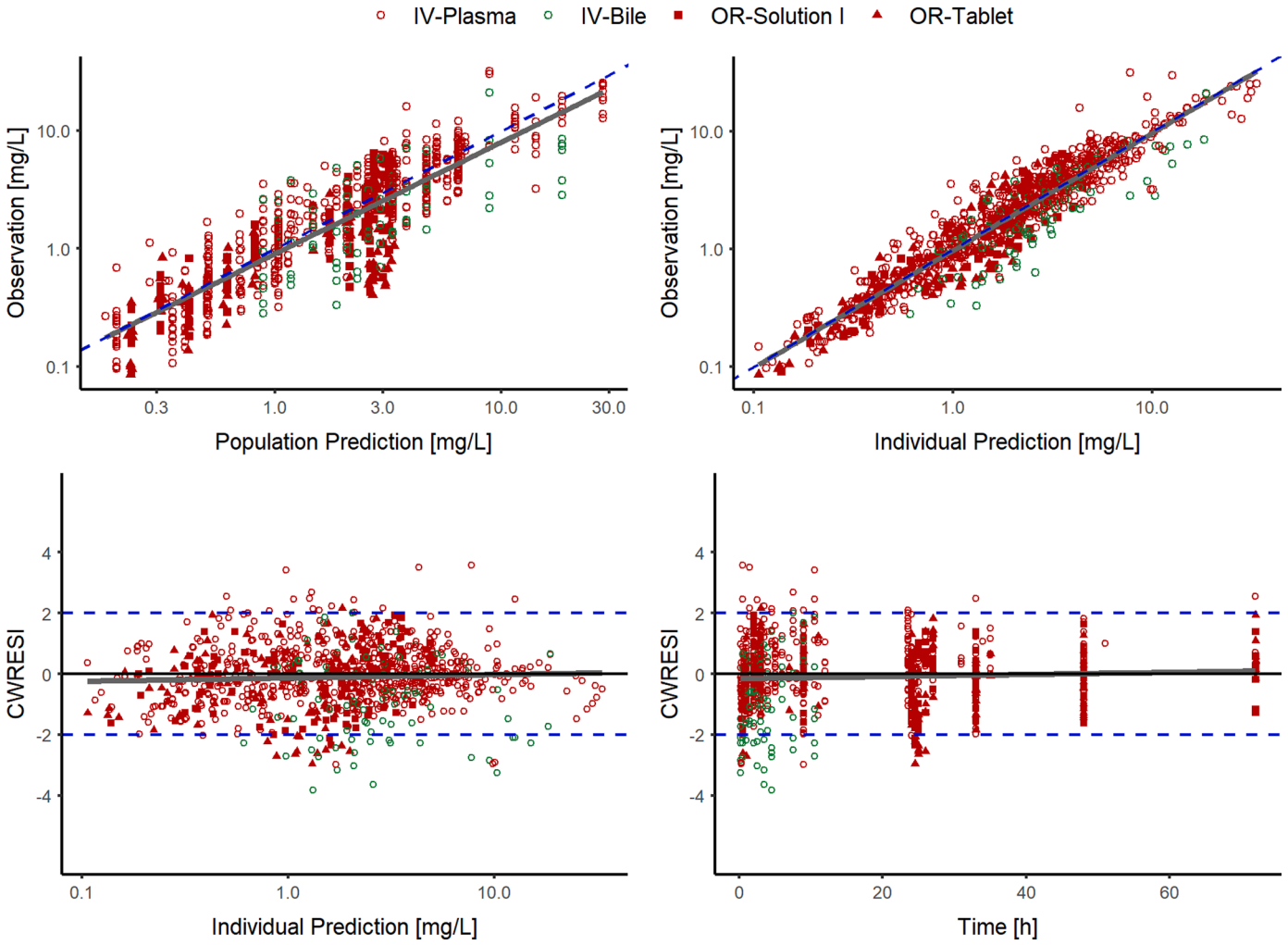


**Fig. 2.** Goodness-of-fit plots of the final population pharmacokinetic model of amiodarone in rats for each oral formulation.
The gray solid line represents the non-linear regression and the blue dotted line represents the line of identity. IWRES: individual weighted residuals, CWRESI: conditional weighted residuals (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article).

(Ibarra et al., 2021; Jain et al., 2011; Lehr et al., 2009; Okour et al., 2018). An alternative parametrization was evaluated, which included a $k_B$ and a first-order constant into the lumen ($k_7$), but did not statistically improved the overall fit. The re-absorption intestinal process once the AM returns into the lumen due to the EHR was assumed to be equal to the initial intestinal absorption after oral AM administration ($k_{a1}$, $k_{a2}$ and $k_{a3}$). A reduced fraction of the drug was distributed into the bile ($F_{bile}$=12.3%), which was calculated as follows (Lehr et al., 2009):

$$F_{bile} = \frac{k_B}{(k_B + k_{10} + k_{12} + K_b)}$$

Where $k_B$ is $1.29 \times 10^1$ $h^{-1}$, $k_{10}$ is $2.98 \times 10^1$ $h^{-1}$, $k_{12}$ is $7.17 \times 10^1$ $h^{-1}$ and $K_b$ is $3.6 \times 10^{-1}$ $Lh^{-1}mg^{-1}$

Inter-individual random effects were associated to $V_2$ (46%), $k_{12}$ (24%), $K_u$ (13%), $k_{a1}$ (39%), and $k_{a2-3}$ (34%), showing a moderate-to-high IIV of PK parameters. Non-diagonal elements were explored but did not statistically improved the model performance. The RUV was 46% using an additive error model for log-transformed observations.

### 3.2. Pharmacokinetic model evaluation

Table 3 lists the estimates of the PK model parameters together with their corresponding precision according the PK model developed (Fig. 1). All PK parameters were statistically significant as the 95% confidence intervals (95% CI) did not include the null value. The results from the model evaluation exercise indicate that the model was capable of capturing the longitudinal profiles of the median and the dispersion of the data based on the pc-VPC (Fig. 2) and the standard GOF plots (Fig. 3).

### 3.3. Simulation-based analysis of unbound/bound fractions of AM

The typical longitudinal ratios between the unbound and bound fraction of AM in the central and peripheral compartments of each OR formulation are depicted in Fig. 4, including dose levels evaluated in the current population PK analysis (12.5 and 25 mg) and extrapolated dose levels (50 and 100 mg) of AM. A rapid decrease in the unbound/bound ratio at both compartments is explained by the binding process of AM, achieving steady-state conditions around 24 h, showing the slow binding process of AM. These results show a slight increase in the unbound fraction with the dose level in the central compartment and irrespective of the OR formulation considered, as expected due to the non-linear binding kinetics of the population PK model. Due to the linear kinetic binding in the peripheral compartment, no differences were observed between the dose levels considered.

## 4. Discussion

AM is highly lipophylic drug, showing a unique pharmacokinetic

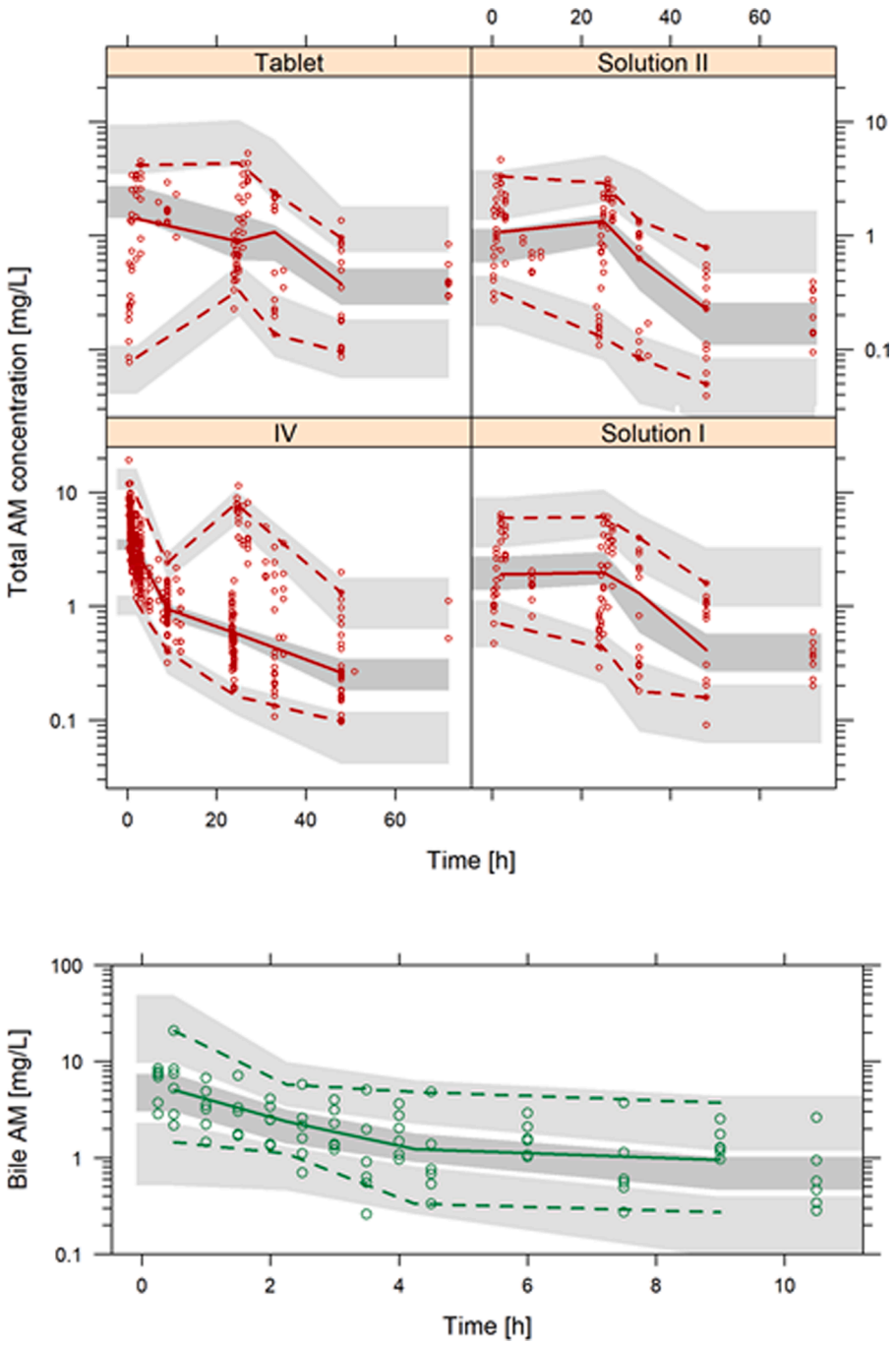


**Fig. 3.** Prediction-corrected visual predictive check of the final population PK model.
Shaded areas represent the 95% prediction intervals of the 2.5th, 50th and 97.5th percentiles of the simulated data. Circles represent amiodarone observations and lines represent the 2.5th, 50th and 97.5th percentiles of the raw data.

profile. There is a good correlation between plasma concentration of AM and its oral maintenance dose and higher plasma concentration of the drug provides a more effective arrhythmia suppression, but it is associated with a higher risk of drug toxicity. Therefore, in routine clinical practice the monitoring of total cumulative dose may be more useful than monitoring the plasma amiodarone levels. Hence, a better knowledge of the pharmacokinetics of AM, both in absorption and elimination, will reduce variability and improve dosage adjustment in patients. In addition, the approved IV formulation of AM contains benzyl alcohol, which is contraindicated in neonates and should be used with caution in infants and children up to 3 years old (Electronic Medicines Compendium, 2022). Therefore, the development of oral formulations able to increase the oral bioavailability of AM are highly needed.

Complex PK processes of drugs, which have not been properly characterized, may increase the IIV of PK parameters and generate unprecise model-predictions. In this sense, quantitative modeling framework should encompass the biological complexity observed in experimental data in order to serve as a valid tool in the decision-making process of the drug development. A population PK model has been successfully applied to characterize the absorption and EHR processes of different OR formulations of AM in rats by adapting a previously population PK model that accounted for the non-linear and linear distribution processes of AM after IV administration. The population PK model assumes different first-order absorption rate constant for each

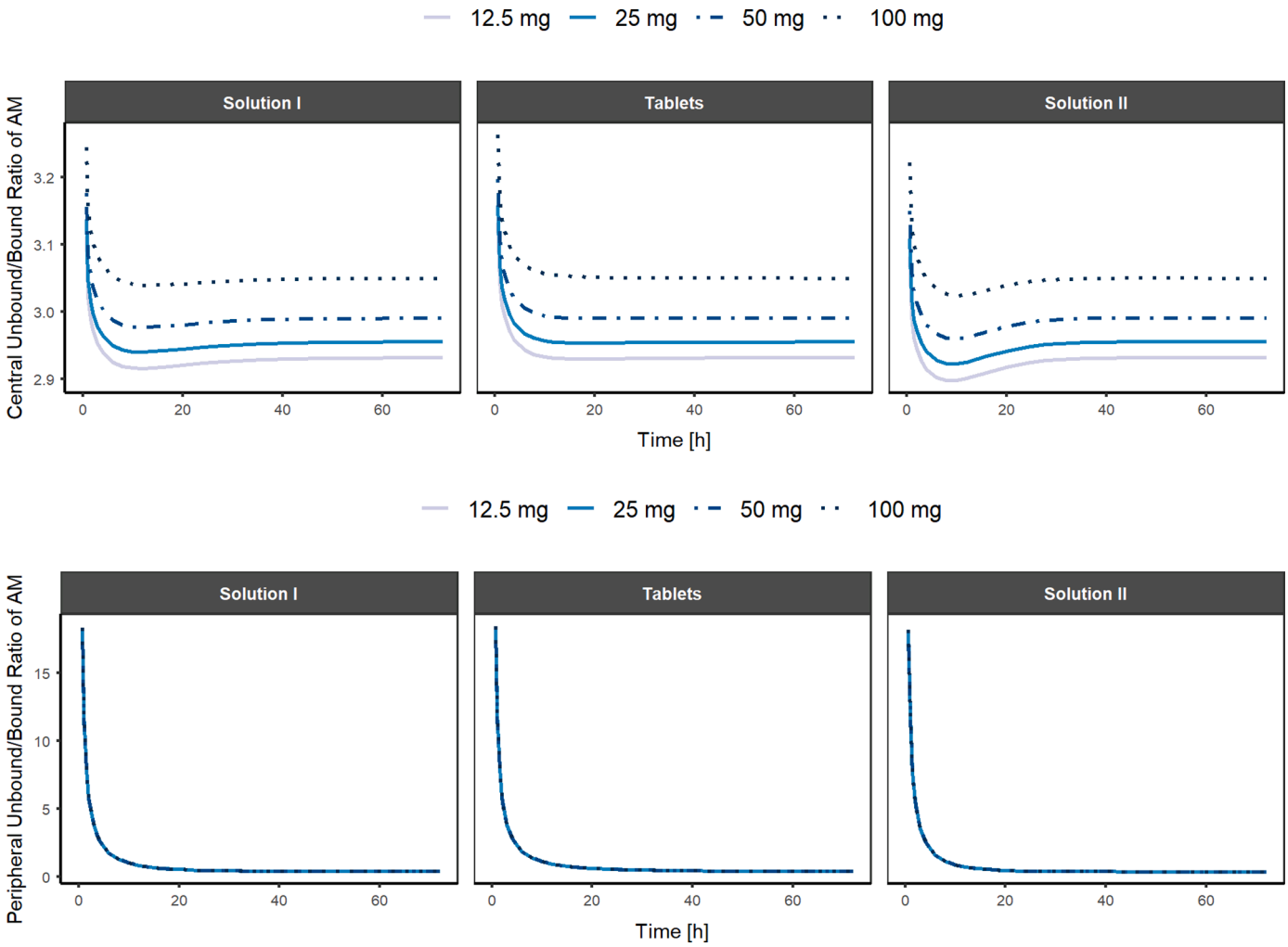


**Fig. 4.** Model predicted unbound/bound ratio of amiodarone in the central (upper) and peripheral (bottom) compartments for each oral formulation after single dose administration of four dose levels.

formulation, demonstrating the contribution of supramicellar concentrations of surfactant (Polysorbate 80) in the improvement of AM oral absorption ($k_{a3}$= 2.05•$10^{-1}$ $h^{-1}$). Similar results were obtained for other lipophilic active principles when co-formulated with surfactants (Alqahtani et al., 2013; Chen et al., 2018; Patel et al., 2015b; Rahman et al., 2016). The current EHR represents the distribution of free AM from the central compartment into the bile and then, into the lumen based on the evidence collected in CC and NC groups. The lack of gallbladder in rats allows assume the continuous emptying of AM into the lumen, which limited the implementation of complex EHR models when the gallbladder exists (Ide et al., 2009; Lehr et al., 2009; Okour et al., 2018; Papathanasiou et al., 2016). The current population PK model quantifies the fraction (12.3%) of AM that suffers EHR and the respective fraction of AM that is metabolized. This result confirms the significant contribution of EHR in the disposition of AM, although due to the absence of experimental observations in the lumen, the fraction excreted via feces could not be estimated.

The development of oral formulations able to increase AM solubility and, ultimately, its absorption rate has been part of research activity recently (Creţeanu et al., 2015; Elgart et al., 2013; Wang et al., 2017). In this sense, an increase of absorption rate of drugs in oral formulation with Polysorbate 80 has been hypothesized to be related to the alteration of the intestinal mucus barrier and mucosal barrier, but these results require further clarification (Martin-Algarra et al., 1995; Zhu et al., 2021). On the other hand, the addition of 5% of Polysorbate 80 resulted in 2.50-fold increase on $k_a$ and 35% increase in its bioavailability compared to Tablet formulation. However, higher concentrations (10%) of Polysorbate 80 in Solution I compared to Tablet formulation only improved by a 1.62-fold the $k_a$ (and 8% its bioavailability), suggesting that increased concentrations of Polysorbate 80 in AM formulations may compromised the absorption process. This phenomenom may be explained by the lipophilic properties of AM and the intramicellar solubilization. Based on this study, 5% concentrations of Polysorbate improve the solubilization of AM in lumen. Higher concentrations of Polysorbate 80 (10%) lead to higher formation of micelles, affecting the release of AM out of the micelles, becoming the PK rate-limiting step process (Martin-Algarra et al., 1995).

Model-based approaches currently represent one of the most demanding and increasing areas in the drug discovery and development process. The ability to determine from a very simplistic perspective to a more detailed and complex manner the mechanisms involved in the time-course of a drug clearly contribute to a more efficient and rationale decision-making process. Thus, the re-use of PK models and its integration to new experimental evidence enhances the potential impact and recognition from adjoining areas. The population PK model externally validates the disposition PK model previously proposed for AM in rats (Campos Moreno et al., 2007) to quantify the contribution of OR formulations and EHR of AM. Similar final parameter estimates were observed between both approaches, demonstrating the adequacy of the population PK model of AM in rats.

Despite the study design characteristics, reduced number of treatment groups evaluated the PK properties of AM after multiple dose

regimens, which might be of relevance in order to better understand how the binding kinetics might be affected when complex and multiple dose levels are administered. Although all formulations contained a polysorbate 80 concentration higher than the CMC, the impact of polysorbate 80 on the AM metabolism could not be assessed due to the lack of hepatic microsomes measurements after its OR and IV administration and the absence of a formulation without polysorbate 80. The complexity of the surgical intervention to collect bile samples resulted in a limited number of observations helping to characterize the EHR process of AM. A 8-fold dose increase (from 12.5 to 100 mg) implies that the unbound/bound ratio of AM only changes by 3% (Fig. 4), indicating that at the usual doses the protein plasma binding is not likely to be saturated. In this sense, it is probable that new formulations that increase the bioavailability of AM do not significantly modify the fractions of free AM in plasma nor the time in which the equilibrium between the free and bound fraction is reached. Alternative preclinical models are encouraged in order to characterize the allometric relationship and the impact of gallbladder emptying that would help to establish accurate and reliable predictions in humans.

## 5. Conclusion

In conclusion, the current population PK model of AM demonstrated the absorption enhancement when AM is formulated with supramicellar concentrations of Polysorbate 80 (Solution II) compared to commercially available oral formulation (Tablet). The study design allowed to characterize the EHR of AM and its contribution in the overall AM disposition. The mathematical framework developed based on preclinical evidence on AM could help to optimize the development of new oral formulations able to increase the oral bioavailability of AM at the preclinical and clinical level and assess whether the impact of EHR processes is similar across different species. Furthermore, this study may contribute to the development of oral solution formulations of AM that could improve the benefit/risk balance of AM and its adherence in pediatric patients.

## CRediT authorship contribution statement

**Karine Rodríguez-Fernández:** Methodology, Software, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Elena Gras-Colomer:** Writing – original draft, Writing – review & editing. **Mónica Climente-Martí:** Supervision, Writing – original draft, Writing – review & editing. **Victor Mangas-Sanjuán:** Methodology, Software, Formal analysis, Writing – original draft, Writing – review & editing. **Matilde Merino-Sanjuán:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing.

## Declaration of Competing Interest

Authors declare no conflict of interest.

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