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Population Pharmacokinetic Model for Cancer Chemoprevention With Sulindac in Healthy Subjects

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Abstract

Sulindac is a prescription-based non-steroidal anti-inflammatory drug (NSAID) that continues to be actively investigated as a candidate cancer chemoprevention agent. To further current understanding of sulindac bioavailability, metabolism, and disposition, we developed a population pharmacokinetic model for the parent compound and its active metabolites, sulindac sulfide, and exisulind. This analysis was based on data from 24 healthy subjects who participated in a bioequivalence study comparing two formulations of sulindac. The complex disposition of sulindac and its metabolites was described by a seven-compartment model featuring enterohepatic recirculation and is the first reported population pharmacokinetic model for sulindac. The derived model was used to explore effects of clinical variables on sulindac pharmacokinetics and revealed that body weight, creatinine clearance, and gender were significantly correlated with pharmacokinetic parameters. Moreover, the model quantifies the relative bioavailability of the sulindac formulations and illustrates the utility of population pharmacokinetics in bioequivalence assessment. This novel population pharmacokinetic model provides new insights regarding the factors that may affect the pharmacokinetics of sulindac and the exisulind and sulindac sulfide metabolites in generally healthy subjects, which have implications for future chemoprevention trial design for this widely available agent.

Keywords

chemoprevention; exisulind; NONMEM; population pharmacokinetics; sulindac

The non-steroidal anti-inflammatory drug (NSAID) sulindac has been widely used for over 30 years as an analgesic agent and in the treatment of various inflammatory conditions.¹ In addition to efficacy in these therapeutic areas, numerous studies have demonstrated that

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Supporting Information

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sulindac exhibits cancer chemopreventive effects, especially in the context of familial adenomatous polyposis (FAP).² The pharmacological activity of sulindac as a chemopreventive agent has been ascribed to two metabolites, sulindac sulfide and sulindac sulfone (exisulind).³ Sulindac sulfide is produced by reduction of the parent sulfoxide via methionine sulfoxide reductase⁴ and is the major sulindac species responsible for the COX-dependent inhibition of prostaglandin synthesis.⁵ Exisulind is formed by cytochrome P450-mediated oxidation and belongs to the class of selective COX-independent pro-apoptotic anti-neoplastic compounds, whose activity is exerted through inhibition of cGMP phosphodiesterases.^{6,7} Although development of exisulind as a stand-alone agent for chemoprevention has been suspended due to toxicities,⁸ investigation of sulindac as a candidate anti-cancer agent was recently re-invigorated by demonstration of remarkable efficacy (in combination with difluoromethylornithine) in a colorectal adenoma prevention trial,⁹ with numerous open studies currently evaluating its chemopreventive and/or chemotherapeutic potential with respect to diverse cancer types.¹⁰

While sulindac was originally approved by the U.S. FDA in 1978,¹¹ pharmacokinetic data for this agent is relatively limited, as compared to other NSAIDs.¹² Previous pharmacokinetic studies focused mainly on the delineation of model-independent pharmacokinetic parameters such as area under the plasma concentration–time curve (AUC) and maximal plasma concentration (C_{max}).³ The strict use of non-compartmental analysis to describe sulindac pharmacokinetics has been attributed to the complex pharmacokinetic behavior of the drug,¹³ including enterohepatic recirculation (EHR), reversible metabolism to the sulfide metabolite and high between-subject variability (BSV).^{3,14} To the best of our knowledge, no compartmental model describing sulindac pharmacokinetics in humans is available in the literature and thus data describing model-based parameters such as volumes of distribution and rate constants are limited for sulindac and its metabolites.

Due to the paucity of comprehensive pharmacokinetic data for sulindac as well as our interest in this agent for cancer chemoprevention, our primary aim was to quantify the metabolism and disposition of sulindac through the use of population-based methods. Using data from an earlier bioequivalence study in generally healthy adults,¹⁵ nonlinear mixed effects modeling was employed to develop the first reported population pharmacokinetic model for sulindac and the active metabolites, sulindac sulfide, and exisulind. This model accounts for the bioavailability of the National Cancer Institute (NCI)—sponsored capsule formulation relative to the commercial tablet formulation and improves upon the earlier non-compartmental analysis of their bioequivalence.¹⁵ As a secondary aim, we used the derived model to explore clinical variables for significant correlations with sulindac pharmacokinetic parameters.

Methods

Study Population and Pharmacokinetic Data

Plasma concentration data from a total of 24 healthy adults was available from an NCI-sponsored and Mayo Clinic Institutional Review Board (IRB)-approved 2×2 crossover study comparing the bioequivalence of an NCI-sponsored capsule formulation to a reference tablet formulation.¹⁵ Baseline clinical covariates for the study participants are

provided in Supplementary Table S1 in the electronic supplementary materials. Plasma samples were collected at baseline and at the following nominal time points following each 150 mg dose: 0.25, 0.5, 1.0, 1.5, 2, 3, 4, 6, 8, and 24 hours. Details describing the analytical assay are provided elsewhere.¹⁵ The lower limit of quantitation (LLOQ) for all sulindac species was 0.05 µg/mL. Sulindac observations below the quantitation limit (BQL) were censored using the M6 method of Beal,¹⁶ whereas metabolite observations were censored using a variation of this method such that all BQL observations were discarded for each individual except those immediately after the last non-BQL observation. This variation avoids the assignment of identical concentrations for sulindac and the metabolites during the absorption phase; a scenario that is unrealistic given the delayed appearance of both metabolites in the plasma compared to the parent drug.^{3,15} Following censoring, 448, 387, and 374 data points for sulindac, sulindac sulfide, and exisulind were available for analysis, respectively.

Population Pharmacokinetic Modeling

Population pharmacokinetic modeling was performed using NONMEM 7 (ICON Development Solutions, Ellicott City, MD) as executed through the software, PsN-Toolkit, Version 3.4.2.¹⁷ NONMEM output was analyzed using Xpose, Version 4.3.2¹⁸ as implemented through the statistical software, R, Version 2.12.2.¹⁹ A composite estimation method employing the iterative two-stage method followed by Monte Carlo importance sampling assisted with mode *a posteriori* estimation was utilized for initial model building. When BSV terms were removed during model development, several parameters could no longer be μ -referenced²⁰ and consequently the first-order conditional estimation method with interaction (FOCE-I) was employed for model refinement, covariate testing and model validation. Model selection was based on prior information regarding the pharmacokinetics of sulindac,³ the likelihood ratio test, goodness-of-fit plots, shrinkage estimates as well as the reasonableness of parameter estimates and their bootstrap distributions.^{21,22}

During model development, a compartmental model was determined simultaneously for sulindac and sulindac sulfide, due to the reversible inter-conversion of these species.³ Following delineation of the model structure for sulindac and sulindac sulfide, observations for exisulind were added and a structural model for this metabolite was ascertained. All kinetic processes were assumed to be first-order and various absorption models were tested including lag, transit,²³ or Weibull models.²⁴ The relative bioavailability of each formulation was assessed using separate absorption parameters for the tablet and capsule, under the assumption that formulation effects influenced only the absorption phase.²² The bioavailability of the tablet formulation was fixed at 100% for all subjects, whereas the relative bioavailability of the capsule was estimated by the parameter, BIO. One, two, and three compartment model structures with or without EHR were tested to describe the distribution and elimination of the various sulindac species and were parameterized using central volumes of distribution and microscopic rate constants. An additional parameter, T_{EHR} , denoting the onset of sulindac release from the EHR compartment, was estimated and EHR release was constrained to be active for 0.75 hour to approximate the mean gall bladder emptying time in healthy individuals.²⁵

The statistical model describing variability in sulindac pharmacokinetics included parameters for between-subject, inter-occasion, and residual unexplained variability (denoted as BSV, IOV, and RUV, respectively). BSV and IOV parameters were modeled using an exponential (log- normal) error model, whereas RUV was modeled with a proportional error structure. Covariance between model parameters was ascertained by investigation of the unstructured Ω matrix and was included on parameters which exhibited correlations with an absolute value > 0.5 .²⁶ For diagonal Ω elements, inclusion was based on the likelihood ratio test with significant Δ OFV based on a modified chi-square distribution for 1 DoF.²²

Correlations between the covariates listed in Supplementary Table S1 and sulindac pharmacokinetic parameters were investigated using generalized additive modeling (GAM) and graphical assessments based on individual *post hoc* BSV parameter estimates for each individual. Covariates identified as influential by either approach were tested for significance via stepwise addition using the likelihood ratio test ($\alpha = 0.05$), with power and fractional change models used for continuous and categorical covariates, respectively.²² Corresponding *P*-values for each significant covariate selected during the addition phase were obtained by stepwise deletion from the final model.

Validation of model parameter estimates was via non- parametric bootstrap ($n = 1,000$), with 5th, 50th, and 95th percentiles generated from only those runs that terminated successfully without estimates near a boundary. Predictive performance of the final model was investigated by simulation of 500 replicates of the initial dataset using median values obtained from the bootstrap. Non-compartmental pharmacokinetic parameters calculated from the observed and simulated data were compared using a two-tailed *t*-test on log-transformed data. For visual assessment, the 5th, 50th, and 95th percentiles of the simulated plasma concentrations were overlaid on top of the observed plasma concentrations for all sulindac species. Additionally, a quantile–quantile (QQ) plot comparing the distributions of simulated and observed $AUC_{0-24 \text{ hour}}$ values for each study participant was generated.

Results

Representative plasma concentration–time profiles for the tablet and capsule formulations (Figure 1) illustrate the plasma profiles of the three sulindac species. The presence of secondary peaks at approximately 6–8 hours post-dose is consistent with the known EHR behavior of the drug.³ As this feature was apparent following administration of either formulation and was observed in at least one of the sulindac species for all subjects, an EHR compartment was included *a priori* in the model structure. Additional prior information regarding the metabolism and disposition of sulindac was considered during model development. Specifically, previous reports demonstrate that conversion of sulindac to exisulind is an irreversible process, whereas conversion to the sulfide form is reversible.²⁷ It has further been reported that inter- conversion is essential for sulindac sulfide elimination since the excretion of this species is negligible.³ Consequently, features reflecting these properties were incorporated into the compartmental model for sulindac and its metabolites, as dictated by graphical and numerical goodness-of-fit criteria.

The final model structure for sulindac, sulindac sulfide, and exisulind is described by Figure 2, along with corresponding differential equations. Key features of this model include a one-compartment model for sulindac, a two-compartment model to describe the behavior of both metabolites, and an EHR compartment which forms a loop between the sulindac central and absorption compartments to account for the secondary peaks present for all sulindac moieties. While an additional EHR peak was putatively identified at approximately 24 hours for three subjects, a second EHR event was not included in the model due to the small number of subjects and limited data in this time region. Absorption of both formulations was best described using a transit model,²³ which was superior to the lag-time and Weibull absorption models (as evidenced by changes in the objective function value (Δ OFV) of –78.82 and –29.93, respectively).

Initial development of the population pharmacokinetic model included BSV terms on all structural model parameters, but several BSV terms were later removed due to low variance estimates, large shrinkage values or were not statistically significant via the likelihood ratio test. BSV was not included in the final model for parameters describing the formation of sulindac sulfide and its peripheral distribution (K_{23} and K_{34}), the peripheral distribution of exisulind (K_{67} and K_{76}), and EHR (K_{25} , K_{51} , and T_{EHR}). Inspection of the unstructured Ω matrix for the remaining BSV terms prompted inclusion of covariance between tablet and capsule MTT, capsule MTT and N, as well as between V_D/F and K_{32} , which resulted in a significant Δ OFV of –69.74. Inclusion of inter-occasion variability (IOV) terms on systemic pharmacokinetic parameters was statistically significant only for the formation of exisulind (K_{26}) as evidenced by the Δ OFV of –59.05. IOV could not be assessed for any absorption parameter as data was available from only one dosing occasion for each formulation. Residual unexplained variability (RUV) was quantified separately for each sulindac moiety and utilized a proportional error structure, consistent with the properties of the analytical assay used for quantification of sulindac and its metabolites.¹⁵ Shrinkage estimates were <25% for all BSV, IOV and RUV terms except for those describing BSV in K_{20} (25.8%) and K_{26} (31.1%). Table 1 provides estimates from the final model for all structural and statistical model parameters along with the median and 90% confidence interval from the non-parametric bootstrap.

Exploratory screening of covariates using individual *post hoc* estimates followed by stepwise addition revealed that only sex, weight, and creatinine clearance were significant at the $\alpha = 0.05$ level. Inclusion of a weight effect to sulindac elimination (K_{20}) and capsule bioequivalence (Cap BIO) decreased BSV in these terms by 0.078 and 0.018, respectively, whereas addition of a correlation between creatinine clearance and V_D/F decreased BSV by 0.101. The sex effect on K_{26} demonstrates that women form approximately 29% less exisulind compared to men and decreased BSV in this parameter by 0.049. In contrast, despite a 1.7-fold increase in capsule MTT for women, inclusion of a sex effect decreased BSV by only 0.002. Together, inclusion of covariates in the final model resulted in a DOFV of 32.19. Table 2 lists the covariate effects on the associated model parameters, the bootstrap median and 90% confidence interval as well as the *P*-value obtained by stepwise deletion, which is provided to aid interpretability.

Goodness-of-fit plots for the final population pharmacokinetic model demonstrate good agreement between the observed and population predicted plasma concentrations for all sulindac moieties and both formulations (Figure 3). Moreover, no trends are seen in the distribution of conditional weighted residuals (CWRES) for any sulindac species when plotted versus population predicted concentration or time post dose and further demonstrate that the bulk of residuals lie within the generally accepted range of ± 2.0 (Supplementary Figure S1). Based on the diagnostic plots, our population pharmacokinetic model is sufficient for describing the plasma concentration–time profiles of sulindac and its metabolites in healthy adults.

The final model estimates (Tables 1 and 2) were validated via non-parametric bootstrap analysis which provided median and 90% confidence intervals for all parameters. Model estimates are in excellent agreement with bootstrap medians and the 90% confidence interval range demonstrates that the majority of parameters were well estimated. Using the bootstrap medians, central clearances of 15.7 L/hour and 1.3 L/hour were derived for sulindac and exisulind, respectively, in excellent agreement with previously reported pharmacokinetic data.^{3,28} A visual predictive check based on the median bootstrap estimates was used to assess the predictive performance of the model (Figure 4) and demonstrates that >90% of observed plasma concentrations lie within the 5th and 95th percentiles of the simulated concentrations. Moreover, no statistically significant differences in non-compartmental parameters (*viz.* $AUC_{0-24 \text{ hour}}$ and C_{max}) were found between simulated and observed data. This is supported by the QQ plot (Figure 4, Panel D) which illustrates the similar distribution of $AUC_{0-24 \text{ hour}}$ values in the original and simulated datasets, albeit with increasing variability at higher AUC values due to the underlying log normal distribution. Taken together, the results of the bootstrap and predictive check demonstrate that the developed model is valid in terms of parameter estimation as well as predictive performance and sufficiently describes the pharmacokinetics of sulindac, exisulind, and sulindac sulfide.

Given the high variability in sulindac pharmacokinetics that was observed in our earlier bioequivalence assessment,¹⁵ we wished to better define the relative bioavailability of the capsule formulation. Parameters included in our population pharmacokinetic model (K_A and BIO , respectively) are provided in Supplementary Table S2 along with corresponding non-compartmental parameters (C_{max} and $AUC_{0-24 \text{ hour}}$) and parameter ratios comparing the test versus reference formulations. The data reveal excellent agreement between model-based and non-compartmental parameters and indicate that the capsule is absorbed significantly faster than the tablet. However, both formulations provided similar exposure to all three sulindac moieties as indicated by the BIO estimate of 1.11 and the simulated capsule to tablet $AUC_{0-24 \text{ hour}}$ ratios of 1.13–1.16. Since these ratios lie in the range of 0.80–1.25, which is used by the FDA to demonstrate bioequivalence,²⁹ our results indicate that the formulations are bioequivalent with respect to overall exposure to sulindac, exisulind, and sulindac sulfide.

Discussion

To our knowledge, the model developed herein represents the first reported population pharmacokinetic model for sulindac. In addition to describing the absorption and complex

disposition of the parent drug, this model delineates the pharmacokinetic behavior of the active metabolites, sulindac sulfide, and exisulind. Moreover, estimates of population variability in model parameters have been ascertained which are useful in providing insight into the differences in sulindac pharmacokinetics between healthy individuals and deconvoluting formulation effects from other sources of pharmacokinetic variability.

The most striking aspect of our compartmental model is the inclusion of an EHR loop for sulindac that sufficiently describes the pharmacokinetic behavior of all three sulindac species. Estimated rates of sulindac elimination into, and release from, the EHR compartment are consistent with previous reports for other drugs.^{30,31} The EHR onset time of 5.9 hours post dose is as expected based on individual plasma concentration–time curves (Figure 1). Note that while the time and magnitude of the EHR peaks were variable from subject to subject, BSV could not be ascertained for associated model parameters. Given the limited samples obtained during the EHR release period and the inability to directly measure concentrations in the gallbladder and gut, data describing variability in the EHR process was limited. This also explains the large bootstrap confidence interval for K_{51} (which represents sulindac release from the EHR compartment). The confidence interval is skewed towards high values, suggesting that gallbladder release may be described as an instantaneous process. However, since EHR is often modeled as a bolus and the model estimate and bootstrap median values were consistent with values reported in previous studies,^{30–32} the uncertainty in the estimation of K_{51} does not appear to adversely affect our model. Accordingly, while we believe that our model sufficiently characterizes the pharmacokinetic behavior of sulindac and its metabolites, we recognize that additional data may eventually support a different model structure.

During model development, the common assumption of identical central V_D for parent drug and metabolites was employed, which is often used when all drug species have similar chemical structures (as is the case for sulindac and its metabolites). A benefit of this approach is that the fractional conversion of parent drug to each metabolite species can be assessed which was of specific interest in this analysis. Under this assumption, comparison of the magnitudes of K_{23} and K_{26} reveal that formation of sulindac sulfide is favored over exisulind. It should be emphasized that although our model indicates a >2-fold higher AUC for sulindac sulfide versus exisulind (Supplementary Table S2), relative exposures to each metabolite will differ between individuals given the variability in sulindac pharmacokinetics. This may be important in dictating the individual efficacy of sulindac therapy, as sulindac sulfide and exisulind are thought to provide anti-cancer benefits through COX-dependent and COX-independent mechanisms, respectively. Since the relative importance of these mechanisms is currently unknown, differences in exposure to exisulind and sulindac sulfide may ultimately prove to be clinically significant.

Given that data from an earlier bioequivalence study was used for model development,¹⁵ our dataset provided a unique opportunity to compare model-based bioequivalence measurements with those derived from non-compartmental methods. In the initial non-compartmental analysis, the formulations were found to be bioequivalent with respect to exposure to sulindac sulfide and exisulind, but not exposure to parent drug. However, significant variability in non-compartmental parameters was observed, suggesting that the

data did not provide sufficient power to demonstrate bioequivalence using standard non-compartmental methods. An advantage to the use of population-based methods for bioequivalence assessment is that this approach separates formulation effects from other sources of pharmacokinetic variability³³ thereby helping to better quantify the relative bioavailability of test and reference formulations. Model-based estimates of rate and extent of exposure (K_A and BIO, respectively) clearly reflect the equivalent non-compartmental measures (C_{max} and AUC) obtained from model-based simulations (Supplementary Table S2). Test-to-reference K_A ratios indicate that the capsule is absorbed significantly faster than the tablet, consistent with the dissolution properties of each formulation. In contrast, the estimate and 90% CI for the BIO parameter fall within the accepted range of 0.80–1.25,²⁹ demonstrating that the formulations provide equivalent exposure to parent drug. The extension of bioequivalence to include equivalent exposure to sulindac illustrates that the earlier non-compartmental analysis was confounded by the significant variability in sulindac pharmacokinetics and supports the use of population-based approaches for bioequivalence assessment.

Because our model was generated using data obtained from generally healthy adults, we conducted an exploratory evaluation of correlations between clinical covariates and pharmacokinetic parameters. Covariate assessment was guided by the “knowledge discovery” method advocated by Ette²⁶ and focused on identification of putative correlations to further inform future sulindac-based chemoprevention trials. However, only body weight, creatinine clearance, and sex were found to be significantly correlated with model parameters, a finding attributed to the small and relatively homogenous study population. The association of body weight with K_{20} is not unexpected as this model parameter describes sulindac elimination and weight is often correlated with drug clearance.²² Given this correlation, allometric scaling of the volume and rate constants may be warranted upon future model refinement. In contrast, the correlation of creatinine clearance with V_D/F is surprising and not easily interpreted. One possible explanation for this correlation may be due to the combined effects of weight and sex, since creatinine clearance calculated by the Cockcroft–Gault equation is a composite parameter based on these clinical variables (as well as age), both of which may affect volume of distribution. Similarly, the basis for increased capsule bioavailability with body weight or an increased mean transit time for capsule absorption in women is unclear. Although it is tempting to attribute the former effect to a greater surface area available for absorption in larger individuals and the latter effect to the significantly longer gastrointestinal transit time in women than men,³⁴ the putative covariate effects should be interpreted cautiously and need to be investigated further before definitive conclusions can be reached.

The most intriguing correlation observed in the covariate analysis is that between sex and K_{26} , which decreased the BSV by approximately 0.05 and suggests that women form 29% less exisulind than men. Interestingly, K_{26} is the only parameter which featured IOV, implying that not only is there a sex difference in the extent of exisulind formation, metabolism from the parent drug differs from dose to dose within the same individual. The physiological basis for these findings may arise from variability in the metabolic pathway involved in exisulind formation, which is catalyzed mainly by CYP1A2.⁴ CYP1A2 is inducible by many exogenous compounds, including all three sulindac moieties,^{35,36} which

may explain the IOV in exisulind formation. Moreover, studies have suggested lower CYP1A2 activity in women,^{34,37} consistent with decreased exisulind exposure. Regardless of the mechanism, it is noteworthy that the variability in exisulind formation may be of therapeutic significance given the activity of this metabolite in chemoprevention and thus further investigation of this feature is indicated.

In summary, we have developed the first reported population pharmacokinetic model for sulindac which describes the metabolism and disposition of sulindac and the active metabolites, sulindac sulfide and exisulind. Our model provides compartmentally based pharmacokinetic information for sulindac which to date has been limited and describes the relative bioavailability of the NCI-sponsored capsule formulation. Although this model has yet to undergo external validation with data from another study (unavailable at the time of model development), the internal validation results support that the derived model appropriately describes the population pharmacokinetics of this agent. Moreover, the high pharmacokinetic variability indicated by our model and the correlations identified between clinical covariates and pharmacokinetic parameters suggest avenues for future study, consistent with the recent international consensus statement that further investigation of sulindac's chemopreventive potential is warranted.³⁸

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.

Representative semi-logarithmic plasma concentration-time profiles of the tablet and capsule formulations for two subjects. Open diamonds, closed circles, and open circles represent the plasma concentrations of sulindac, sulindac sulfide, and exisulind, respectively, whereas the dotted line indicates the lower limit of quantitation for all sulindac moieties.

Model Equations:

$$dX_1/dt = \text{TRANSIT} - K_a \cdot X_1 + K_{51} \cdot X_5 \cdot \text{FLAG}$$

$$dX_2/dt = K_a \cdot X_1 + K_{32} \cdot X_3 - (K_{20} + K_{23} + K_{25} + K_{26}) \cdot X_2$$

$$dX_3/dt = K_{23} \cdot X_2 + K_{43} \cdot X_4 - (K_{34} + K_{32}) \cdot X_3$$

$$dX_4/dt = K_{34} \cdot X_3 - K_{43} \cdot X_4$$

$$dX_5/dt = K_{25} \cdot X_2 - K_{51} \cdot X_5 \cdot \text{FLAG}$$

$$dX_6/dt = K_{26} \cdot X_2 + K_{76} \cdot X_7 - (K_{60} + K_{67}) \cdot X_6$$

$$dX_7/dt = K_{67} \cdot X_6 - K_{76} \cdot X_7$$

Figure 2.

Compartmental model for sulindac, sulindac sulfide, and exisulind. The number and description of each compartment is given in the figure, with corresponding model equations. FLAG refers to an indicator variable that equals 1 when the EHR compartment is active, which is between times T_{EHR} and $T_{\text{EHR}} + 0.75$ hour, and is 0 at all other times. The absorption of both the tablet and capsule formulations is given by TRANSIT, which refers to the transit compartment model of Savic et al.²³ and is described by N , the number of transit compartments and MTT , the mean transit time.

Figure 3.

Observed versus population predicted plasma concentrations for sulindac, sulindacsulfide, and exisulind (Panels A, B, and C, respectively). The solid line indicates the line of identity and the data for the tablet and capsule formulations are given by the closed and open circles, respectively.

Figure 4.

Visual predictive check (VPC) for sulindac and its metabolites. Panels A, B, and C depict semi-logarithmic plasma concentration-time plots of simulated and observed data for sulindac, sulindac sulfide, and exisulind, respectively, whereas Panel D depicts the overlaid QQ plot of simulated versus observed $\text{AUC}_{0-24 \text{ hour}}$ for all sulindac species. In Panels A–C, the closed and open circles depict data for the tablet and capsule formulations, respectively, the dotted line indicates LLOQ/2, the dashed line indicates the median plasma concentrations of the simulated data and the solid lines indicate the 5th and 95th percentiles of the simulated data. The solid line in Panel D indicates the line of unity, whereas the gray lines depict the simulation results from 500 replicates of the original dataset.

Table 1**Final Model Parameter Estimates and Bootstrap Results**

Parameter	Model Estimate ^a	Bootstrap
		Median (90% CI)
Structural model parameters		
Tablet K _A (h ⁻¹)	0.667	0.67 (0.603, 0.749)
Tablet MTT (h)	0.845	0.839 (0.67, 1.05)
Tablet N	9.11	9.18 (6.45, 12.7)
Capsule K _A (h ⁻¹)	1.08	1.09 (1.01, 1.15)
Capsule MTT (h)	0.427	0.433 (0.330, 0.568)
Capsule N	15.5	15.4 (9.71, 24.6)
Capsule BIO	1.12	1.11 (1.06, 1.17)
Vd/F (L)	4.63	4.60 (3.97, 5.29)
K ₂₀ (h ⁻¹)	3.41	3.39 (2.95, 4.00)
K ₂₃ (h ⁻¹)	1.25	1.25 (1.14, 1.36)
K ₃₂ (h ⁻¹)	0.52	0.512 (0.429, 0.612)
K ₃₄ (h ⁻¹)	1.65	1.66 (1.46, 1.84)
K ₄₃ (h ⁻¹)	0.326	0.327 (0.287, 0.372)
K ₂₅ (h ⁻¹)	0.182	0.190 (0.114, 0.302)
K ₅₁ (h ⁻¹)	9.46	9.84 (1.68, 9640)
T _{chr} (h)	5.88	5.89 (5.72, 5.966)
K ₂₆ (h ⁻¹)	0.496	0.492 (0.441, 0.557)
K ₆₀ (h ⁻¹)	0.282	0.278 (0.243, 0.326)
K ₆₇ (h ⁻¹)	1.22	1.20 (1.04, 1.48)
K ₇₆ (h ⁻¹)	0.304	0.301 (0.263, 0.361)
Statistical model parameters		
BSV in Tablet K _a	0.235	0.221 (0.126, 0.311)
BSV in Tablet MTT	0.692	0.668 (0.501, 0.826)
BSV in Tablet N	0.950	0.892 (0.596, 0.501)
BSV in Capsule K _a	0.176	0.167 (0.095, 0.239)
BSV in Capsule MTT	0.795	0.773 (0.597, 0.932)
BSV in Capsule N	1.39	1.35 (1.06, 1.66)
BSV in Capsule BIO	0.110	0.100 (0.063, 0.138)
BSV in V _d /F	0.152	0.145 (0.077, 0.192)
BSV in K ₂₀	0.141	0.138 (0.063, 0.210)
BSV in K ₃₂	0.490	0.471 (0.327, 0.607)
BSV in K ₄₃	0.261	0.259 (0.141, 0.358)
BSV in K ₂₆	0.176	0.173 (0.063, 0.253)
BSV in K ₆₀	0.391	0.383 (0.276, 0.487)

Parameter	Model Estimate ^a	Bootstrap
		Median (90% CI)
Covariance (Tab MTT – Cap MTT)	0.304 (r = 0.55)	0.282 (0.105, 0.484)
Covariance (Cap MTT – Cap N)	–0.706 (r = –0.64)	–0.668 (–1.08, –0.347)
Covariance (V _d /F – K ₃₂)	–0.038 (r = –0.55)	–0.036 (–0.071, –0.005)
IOV in K ₂₆	0.245	0.239 (0.173, 0.305)
RUV in sulindac	0.316	0.315 (0.285, 0.344)
RUV in sulindac sulfide	0.265	0.261 (0.235, 0.290)
RUV in exisulind	0.161	0.158 (0.141, 0.176)

CV, coefficient of variation; r, correlation coefficient; RUV, residual unexplained variability; BSV, between-subject variability; IOV, inter-occasion variability.

^aBSV, IOV, and RUV are reported as standard deviations, calculated as the square root of the variance (ω^2) which is the estimated model parameter.

Table 2

Parameter Estimates for Covariates Included in the Final Model

Parameter	θ Estimate	Bootstrap		<i>P</i> -value ^a
		Median	90% CI	
Body weight				
K ₂₀	0.578	0.595	(0.128, 1.132)	.016
Capsule BIO	0.344	0.345	(0.149, 0.636)	.019
Sex				
K ₂₆	0.709	0.705	(0.626, 0.799)	.015
Capsule MTT	1.698	1.669	(1.186, 2.242)	.032
Creatinine clearance				
V _d /F	0.512	0.526	(0.206, 0.785)	.006

^a *P*-value calculated by stepwise deletion from final model using the Likelihood Ratio Test.