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Technical Note

Mean Residence Times of Multicompartmental Drugs Undergoing Reversible Metabolism

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INTRODUCTION

The application of area (1,2) and moment analysis (3) to reversible metabolism has yielded direct and simple methods of calculating clearances, volumes of distribution, and recycling parameters. Recently, using a stochastic approach, Aarons (4) elucidated the correct mean residence time in the body (MRT) for drugs undergoing reversible metabolism. However, this work was limited to the one-compartment model for drug and metabolite. The meaning of the MRT and the ratio of the first to the zeroth moments of the plasma concentration–time curve (AUMC/AUC) of drugs subject to reversible metabolism requires examination and clarification for linear, multicompartment distribution of drug and metabolite. We have extended Aarons' approach to such drugs (Fig. 1).

THEORETICAL

For a drug (p) and its interconversion metabolite (m) both following a two-compartment model with central (Vc) and peripheral (V_T) compartment volumes (Fig. 1), the rates of change of drug and metabolite plasma concentrations (C_p and C_m) and tissue concentrations (C_{Tp} and C_{Tm}) can be described by the following equations:

$$V_{Tp} \cdot dC_{Tp}/dt = -k_{31} \cdot V_{Tp} \cdot C_{Tp} + k_{13} \cdot Vc_p \cdot C_p \quad (1)$$

$$Vc_p \cdot dC_p/dt = k_{31} \cdot V_{Tp} \cdot C_{Tp} - k_1 \cdot Vc_p \cdot C_p + k_{21} \cdot Vc_m \cdot C_m \quad (2)$$

$$Vc_m \cdot dC_m/dt = k_{12} \cdot Vc_p \cdot C_p - k_2 \cdot Vc_m \cdot C_m + k_{42} \cdot V_{Tm} \cdot C_{Tm} \quad (3)$$

$$V_{Tm} \cdot dC_{Tm}/dt = k_{24} \cdot Vc_m \cdot C_m - k_{42} \cdot V_{Tm} \cdot C_{Tm} \quad (4)$$

where the rate constants are the exit clearance/volume ratios for each compartment (e.g., $k_{10} = CL_{10}/Vc_p$), and summary rate constants are $k_1 = k_{10} + k_{12} + k_{13}$, and $k_2 = k_{20} + k_{21} + k_{24}$. (The above equations are ordered for ease of matrix analysis.) Based on the stochastic approach (5,6), from Eqs. (1)–(4) it follows that mean residence times for drug and metabolite in the body can be calculated as (see Appendix)

$$MRT_p^p = CL_{22} \cdot V_{ss}^p/(CL_{11} \cdot CL_{22} - CL_{12} \cdot CL_{21}) \quad (5)$$

$$MRT_m^p = CL_{12} \cdot V_{ss}^m/(CL_{11} \cdot CL_{22} - CL_{12} \cdot CL_{21}) = MRT_m^m \cdot (CL_{12}/CL_{11}) \quad (6a,b)$$

$$MRT_p^m = CL_{21} \cdot V_{ss}^p/(CL_{11} \cdot CL_{22} - CL_{12} \cdot CL_{21}) = MRT_p^p \cdot (CL_{21}/CL_{22}) \quad (7a,b)$$

$$MRT_m^m = CL_{11} \cdot V_{ss}^m/(CL_{11} \cdot CL_{22} - CL_{12} \cdot CL_{21}) \quad (8)$$

where the parameter superscripts for p and m refer to the dosed compound and the subscripts represent the measured compound, the $V_{ss} = V_c + V_T$ for each compound, and summary clearances are $CL_{11} = CL_{10} + CL_{12}$, and $CL_{22} = CL_{20} + CL_{21}$. These MRT parameters are interpreted as the average interval of time that the drug or metabolite spends in the body before irreversibly leaving the central compartment. Based on mass balance relationships, the following equations have been obtained previously (1–3):

$$Dose^p = CL_{10} \cdot AUC_p^p + CL_{20} \cdot AUC_m^p \quad (9)$$

$$Dose^m = CL_{20} \cdot AUC_m^m + CL_{10} \cdot AUC_p^m \quad (10)$$

$$Dose^p = CL_{11} \cdot AUC_p^p - CL_{21} \cdot AUC_m^p \quad (11)$$

$$Dose^m = CL_{22} \cdot AUC_m^m - CL_{12} \cdot AUC_p^m \quad (12)$$

From Eqs. (9)–(12), it follows that

$$AUC_p^p = Dose^p \cdot CL_{22}/(CL_{11} \cdot CL_{22} - CL_{12} \cdot CL_{21}) \quad (13)$$

$$AUC_m^p = Dose^p \cdot CL_{12}/(CL_{11} \cdot CL_{22} - CL_{12} \cdot CL_{21}) \quad (14)$$

$$AUC_p^m = Dose^m \cdot CL_{21}/(CL_{11} \cdot CL_{22} - CL_{12} \cdot CL_{21}) \quad (15)$$

$$AUC_m^m = Dose^m \cdot CL_{11}/(CL_{11} \cdot CL_{22} - CL_{12} \cdot CL_{21}) \quad (16)$$

Combining Eqs. (5) and (13), (6a) and (14), (7a) and (15), and (8) and (16), separately yields

$$MRT_p^p = V_{ss}^p \cdot AUC_p^p/Dose^p \quad (17)$$

$$MRT_m^p = V_{ss}^m \cdot AUC_m^p/Dose^p \quad (18)$$

$$MRT_p^m = V_{ss}^p \cdot AUC_p^m/Dose^m \quad (19)$$

$$MRT_m^m = V_{ss}^m \cdot AUC_m^m/Dose^m \quad (20)$$

These relationships provide the means of calculating MRT from experimental data. Also of interest are the MRTc parameters, which are defined as the average interval of time

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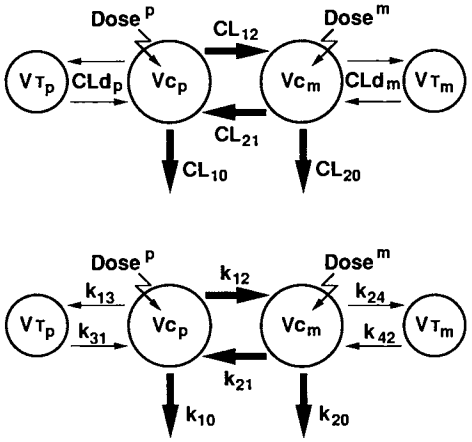

Fig. 1. Two-compartment models of reversible drug metabolism based on metabolic (heavy arrows, CL_{ij}) and distribution (thin arrows, CL_d) clearances (top) or rate constants for metabolism and distribution (bottom), where k_{ij} (i = 1, 2, 3, or 4; j = 0, 1, 2, 3, or 4) are the first-order rate constants. Vc_p, Vc_m, V_{Tp}, and V_{Tm} are the apparent volumes of distribution of the central (c) and tissue (T) compartments of the drug (p) and its metabolite (m).

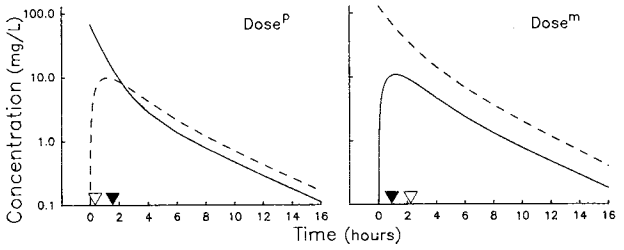

Fig. 2. Simulated concentration–time profiles for the two-compartment model of reversible drug metabolism following separate bolus doses of parent drug and metabolite. Parameter values are listed under Experimental. Lines depict profiles of parent drug (——) and metabolite (---). Triangles denote MRTs of parent drug (▼) and metabolite (▽).

spent by the compound in the central compartment in all of its passages through it. These parameters can be calculated from equations similar to Eqs. (5)–(8) with V_c substituted for V_{ss}. It can be shown that practical methods of generating MRTc values are (see Appendix)

$$MRTc_p^p = Vc_p \cdot AUC_p^p/Dose^p = AUC_p^p/C_p^p(0) \quad (21a,b)$$

$$MRTc_m^p = Vc_m \cdot AUC_m^p/Dose^p = MRTc_m^m \cdot (CL_{12}/CL_{11}) \quad (22a,b)$$

$$MRTc_p^m = Vc_p \cdot AUC_p^m/Dose^m = MRTc_p^p \cdot (CL_{21}/CL_{22}) \quad (23a,b)$$

$$MRTc_m^m = Vc_m \cdot AUC_m^m/Dose^m = AUC_m^m/C_m^m(0) \quad (24a,b)$$

where $C_p^p(0)$ and $C_m^m(0)$ are zero-time concentrations of drug and metabolite after iv dosing. The first moment/area ratios are

$$AUMC_p^p/AUC_p^p = MRT_p^p + (EE - 1) \cdot V_{ss}^m/CL_{22} \quad (25)$$

$$AUMC_m^p/AUC_m^p = AUMC_p^m/AUC_p^m = MRT_p^p + MRT_m^m \quad (26a,b)$$

$$AUMC_m^m/AUC_m^m = MRT_m^m + (EE - 1) \cdot V_{ss}^p/CL_{11} \quad (27)$$

where EE is the Exposure Enhancement parameter, which is defined (3) as

$$EE = 1 + \frac{CL_{12} \cdot CL_{21}}{CL_{10} \cdot CL_{21} + CL_{20} \cdot CL_{12} + CL_{10} \cdot CL_{20}} \quad (28)$$

EXPERIMENTAL

Based on separate intravenous bolus administration of drug and metabolite, plasma concentrations of both compounds (Fig. 2) were generated by numerical integration of Eqs. (1)–(4); using NONLIN84 (7). Simulated data were obtained by assigning numerical values of: $Dose^p$ (5 mg) or $Dose^m$ (5 mg), Vc_p (73.4 liters), Vc_m (39.0 liters), V_{Tp} (40.0 liters), V_{Tm} (20.0 liters), k_{10} (0.817 hr^{-1}), k_{20} (0.246 hr^{-1}), k_{12} (0.188 hr^{-1}), k_{21} (0.385 hr^{-1}), k_{13} (0.123 hr^{-1}), k_{31} (0.300 hr^{-1}), k_{24} (0.103 hr^{-1}), and k_{42} (0.400 hr^{-1}). These parameters were chosen to provide adequate discrimination of the behavior of the drug and metabolite. The values of AUC and AUMC were calculated using the LAGRAN program (8). Values for MRT and MRTc were generated from the above parameters using Eqs. (17)–(24).

RESULTS

Simulations were performed to demonstrate the behavior of drug and metabolite and the relationships between MRT and AUMC/AUC parameters. Figure 2 presents a plot of the simulated concentration–time profiles for drug and metabolite. The compounds given by bolus administration show a multiexponential decline in their central compartments, while the paired metabolites show a formational/distribution phase attaining a maximum concentration, followed by the multiexponential decline. As expected for a linear, equilibrating system, all curves eventually attain a terminal phase with parallel slopes.

Table I lists the mean time and AUMC/AUC values calculated using Eqs. (17)–(27). Values of MRTc for the dosed compounds range from 1.20 to 1.78 hr. Corresponding values of MRT_p^p and MRT_m^m are longer, at 1.58 and 2.25 hr. It can be noted that the sum of MRT_p^p and MRT_m^m equals 3.83 hr, which is identical to that of either $AUMC_m^p/AUC_m^p$ or $AUMC_p^m/AUC_p^m$. This is expected as seen from Eq. (26). In addition, the values of $AUMC_p^p/AUC_p^p$ and $AUMC_m^m/AUC_m^m$ are 1.84 and 2.43 hr, which can also be obtained from Eqs. (25) and (27) when the EE value of the drug/metabolite pair is considered.

DISCUSSION

Equations for MRT and AUMC/AUC parameters of drug and metabolite obeying two-compartment models and

Table I. Comparison of the Mean Residence Time and AUMC/AUC Values for a Two-Compartment System.

Compound		Hours		
Administered, i	Measured, j	$MRTc_j^i$	MRT_j^i	$AUMC_j^i/AUC_j^i$
p	p	1.20	1.58	1.84
p	m	0.33	0.42	3.83
m	p	0.68	0.96	3.83
m	m	1.78	2.25	2.43

subject to reversible metabolism have been derived. According to Eqs. (17)–(20), the MRT parameters can be calculated from the steady-state volume of distribution, AUC, and dose of the administered compound but they are actual functions of V_{ss} and various clearance values as shown in Eqs. (5)–(8). It is of interest to observe that the true MRT in this situation is the quotient of the V_{ss} and the *apparent* clearance, where the latter is Dose/AUC and is related to the four intrinsic metabolic clearances of drug and metabolite (3). Analogous expressions for MRT have been derived for drugs behaving linearly or nonlinearly and without undergoing reversible metabolism (9). Equations to calculate V_{ss}^{p} and V_{ss}^{m} have been derived previously based on AUC and AUMC values (3). This report provides the means of calculating the four essential MRTs noncompartmentally using Eqs. (17)–(20) and thus allows these relationships to apply to reversible models with any number of peripheral compartments for either drug or metabolite. As indicated in previous reports (1–3), the solution of this system requires separate administration and measurement of drug and metabolite AUC and AUMC values.

It has been appreciated that the MRT of a compound subject to reversible metabolism is contaminated by the disposition behavior of its metabolite partner (10), but no equation has been derived to demonstrate clearly this kind of "contamination." The stochastic approach presented here and previously (4) permits estimates of mean residence time of the metabolic pair by utilizing matrix inversion of the coefficients of the differential equations. As shown in Eqs. (5) and (7), MRT_p^p and MRT_p^m indeed depend partly on the disposition kinetics of its interconversion metabolite. Similarly, MRT_m^m and MRT_m^p are influenced by the disposition kinetics of the parent compound [Eqs. (6) and (8)] as well as V_{ss}^{m}.

According to Eqs. (6b) and (7b), MRT_m^p equals MRT_m^m times the fraction of the dosed parent drug that was converted to metabolite (CL_{12}/CL_{11}) and MRT_p^m equals MRT_p^p times the fraction of the dosed metabolite that was converted to the parent drug (CL_{21}/CL_{22}). Similar relationships also exist between $MRTc_m^p$ and $MRTc_m^m$ [Eq. (22b)] as well as between $MRTc_p^m$ and $MRTc_p^p$ [Eq. (23b)]. Since, for a bolus drug subject to reversible metabolism, MRT_p^p and MRT_m^p are the MRTs of the drug in the body measured as the drug itself and its metabolite partner, the total MRT of the drug present in the body as its drug/metabolite pair equals the sum of MRT_p^p and MRT_m^p. Similarly, when the corresponding metabolite is dosed directly its total MRT in the body equals the sum of MRT_m^m and MRT_p^m. Since the sum of MRT_p^p and MRT_m^p may not be equal to the sum of MRT_m^m and MRT_p^m, the drug and its metabolite when dosed directly and separately do not necessarily yield the same total MRT in the body. Thus, when a parent compound and its interconversion metabolite have similar pharmacological activity and the mean residence time in the body is a good indicator of target tissue persistency of both compounds, the one with longer total MRT may be a better drug candidate.

According to Eqs. (25) and (27), $AUMC_p^p/AUC_p^p$ overestimates MRT_p^p by $(EE - 1) \cdot V_{ss}^m/CL_{22}$, while $AUMC_m^m/AUC_m^m$ overestimates MRT_m^m by $(EE - 1) \cdot V_{ss}^p/CL_{11}$. This was also demonstrated by our computer simulations (Table I). As shown in Eq. (26) and Table I, $AUMC_m^p/AUC_m^p$ and $AUMC_p^m/AUC_p^m$ equal the sum of MRT_p^p and MRT_m^m. Consequently, for a bolus-dosed drug subject to reversible metabolism, although moment analysis does not directly provide the true MRT_p^p and MRT_m^m, it does permit estimates of the sum of MRT_p^p and MRT_m^m. The previous use of MRT = AUMC/AUC for a reversible drug/metabolite system [Eqs. (35)–(37) in Ref. 3] was thus incorrect.

Equations to calculate MRTc parameters have also been derived. According to Eqs. (21)–(24), these parameters can be generally calculated as the quotient of $Vc \cdot$ AUC and dose but only partly as AUC/$C(0)$. Rescigno and Gurpide (11) originally defined MRTc = AUC/$C(0)$ for an iv-administered drug and it is reasonable that this relationship holds in the face of reversible metabolism. However, the definition of MRTc for the formed compound is unique. For a drug obeying the one-compartment model and subject to reversible metabolism, the MRTc parameters, of course, equal the corresponding MRTs, making the latter easy to calculate. Expressions for these MRTs have been derived previously as specific functions of first-order rate constants (4). The MRTc parameters are of value for several reasons. They permit the estimation of the mean interconversion time (MIT) parameter, which is the mean time for a parent drug molecule (or for a metabolite molecule) to be converted to a metabolite molecule (or a parent drug molecule) and to be back-converted once. The MRTc are also indicators of sampling compartment persistency of a drug/metabolite pair. Moreover, together with the MRTs, they allow calculation of the mean transit times of a metabolite pair. Application of the mean interconversion time and the mean transit time concepts to corticosteroid disposition in rabbits will be addressed in a subsequent report.

It should be noted that, although the equations derived in this work have been based only on the two-compartment model, they are meaningful for drugs and metabolites obeying any multiperipheral compartment model with elimination from the central compartment and subject to reversible metabolism and provide a link between the stochastic approach to calculate the mean residence times and the noncompartmental approach for these mean times. The MRT and MRTc parameters are functions of the steady-state (for MRT) or central (for MRTc) volumes of distribution, specific AUC values, and dose and thus can be readily generated from typical experimental data where both drug and metabolite have been administered. The AUC and AUMC values are needed for noncompartmental calculation of V_{ss} and clearance values. Relationships between MRT and AUMC/AUC parameters are demonstrated for drug and its interconversion metabolite using computer simulations.

APPENDIX

The coefficients of Eqs.(1)–(4) may be written as one matrix, **B**:

$$\mathbf{B} = \begin{vmatrix} -k_{31} & k_{13} & 0 & 0 \\ k_{31} & -k_1 & k_{21} & 0 \\ 0 & k_{12} & -k_2 & k_{42} \\ 0 & 0 & k_{24} & -k_{42} \end{vmatrix} \qquad \text{(A1)}$$

The determinant of **B**, B, can be obtained from **B** as

$$B = k_{31} \cdot k_{42} \cdot (k_{11} \cdot k_{22} - k_{12} \cdot k_{21}) = k_{31} \cdot k_{42} \cdot k_b \quad \text{(A2a,b)}$$

where $k_b = k_{11} \cdot k_{22} - k_{12} \cdot k_{21}$. The negative of the inverted matrix, $-\mathbf{B}^{-1}$ is shown as Eq. (A3) below:

$$-\mathbf{B}^{-1} = \begin{vmatrix} -B_{11}/B & -B_{21}/B & -B_{31}/B & -B_{41}/B \\ -B_{12}/B & -B_{22}/B & -B_{32}/B & -B_{42}/B \\ -B_{13}/B & -B_{23}/B & -B_{33}/B & -B_{43}/B \\ -B_{14}/B & -B_{24}/B & -B_{34}/B & -B_{44}/B \end{vmatrix} \quad \text{(A3)}$$

where $B_{ij}(i,j = 1\text{–}4)$ are the adjoints of the minor matrix for row i and column j of B. It can be readily shown that

$$B_{21} = -k_{13} \cdot k_{22} \cdot k_{42} \quad \text{(A4)}$$
$$B_{22} = -k_{31} \cdot k_{22} \cdot k_{42} \quad \text{(A5)}$$
$$B_{23} = -k_{31} \cdot k_{12} \cdot k_{42} \quad \text{(A6)}$$
$$B_{24} = -k_{31} \cdot k_{12} \cdot k_{24} \quad \text{(A7)}$$
$$B_{31} = -k_{13} \cdot k_{21} \cdot k_{42} \quad \text{(A8)}$$
$$B_{32} = -k_{31} \cdot k_{21} \cdot k_{42} \quad \text{(A9)}$$
$$B_{33} = -k_{42} \cdot k_{11} \cdot k_{31} \quad \text{(A10)}$$
$$B_{34} = -k_{24} \cdot k_{11} \cdot k_{31} \quad \text{(A11)}$$

According to the stochastic approach (5,6), the MRTs of the drug obeying the two-compartment model and subject to reversible metabolism can be calculated as follows:

$$MRT_p^p = -(B_{21} + B_{22})/B \quad \text{(A12)}$$
$$MRT_m^p = -(B_{23} + B_{24})/B \quad \text{(A13)}$$
$$MRT_p^m = -(B_{31} + B_{32})/B \quad \text{(A14)}$$
$$MRT_m^m = -(B_{33} + B_{34})/B \quad \text{(A15)}$$

Substituting Eqs. (A2b) and (A4)–(A11) into Eqs. (A12)–(A15) yields

$$MRT_p^p = k_{22} \cdot [1 + (k_{13}/k_{31})]/k_b \quad \text{(A16)}$$
$$MRT_m^p = k_{12} \cdot [1 + (k_{24}/k_{42})]/k_b \quad \text{(A17)}$$
$$MRT_p^m = k_{21} \cdot [1 + (k_{13}/k_{31})]/k_b \quad \text{(A18)}$$
$$MRT_m^m = k_{11} \cdot [1 + (k_{24}/k_{42})]/k_b \quad \text{(A19)}$$

The traditional equations for V_{ss}^p and V_{ss}^m are

$$V_{ss}^p = [1 + (k_{13}/k_{31})] \cdot Vc_p \quad \text{(A20)}$$
$$V_{ss}^m = [1 + (k_{24}/k_{42})] \cdot Vc_m \quad \text{(A21)}$$

Multiplying the right-hand side of Eqs. (A16)–(A19) with $Vc_p \cdot Vc_m/Vc_p \cdot Vc_m$, substituting Eqs. (A20) and (A21) into the results, and expressing the volume · rate constant terms as clearances yields Eqs. (5), (6a), (7a), and (8). Dividing Eq. (7a) by Eq. (5) as well as dividing Eq. (6a) by Eq. (8) yields

$$MRT_p^m/MRT_p^p = CL_{21}/CL_{22} \quad \text{(A22)}$$

and

$$MRT_m^p/MRT_m^m = CL_{12}/CL_{11} \quad \text{(A23)}$$

Rearranging Eqs. (A22) and (A23) yields Eqs. (7b) and (6b).

Similarly, according to the stochastic approach (5,6), the MRTc values can be calculated as follows:

$$MRTc_p^p = -B_{22}/B \quad \text{(A24)}$$
$$MRTc_m^p = -B_{23}/B \quad \text{(A25)}$$
$$MRTc_p^m = -B_{32}/B \quad \text{(A26)}$$
$$MRTc_m^m = -B_{33}/B \quad \text{(A27)}$$

Substituting Eqs. (A5), (A6), (A9), and (A10) into Eqs. (A24)–(A27) and using similar derivation techniques mentioned above for MRTs yields Eqs. (21)–(24) and the following equations:

$$MRTc_p^p = CL_{22} \cdot Vc_p/(CL_{11} \cdot CL_{22} - CL_{12} \cdot CL_{21}) \quad \text{(A28)}$$
$$MRTc_m^p = CL_{12} \cdot Vc_m/(CL_{11} \cdot CL_{22} - CL_{12} \cdot CL_{21}) \quad \text{(A29)}$$
$$MRTc_p^m = CL_{21} \cdot Vc_p/(CL_{11} \cdot CL_{22} - CL_{12} \cdot CL_{21}) \quad \text{(A30)}$$
$$MRTc_m^m = CL_{11} \cdot Vc_m/(CL_{11} \cdot CL_{22} - CL_{12} \cdot CL_{21}) \quad \text{(A31)}$$

The following equations can also be derived from Eqs. (1)–(4):

$$AUMC_p^p = \frac{Dose^p \cdot (V_{ss}^p \cdot CL_{22}^2 + V_{ss}^m \cdot CL_{12} \cdot CL_{21})}{(CL_{11} \cdot CL_{22} - CL_{12} \cdot CL_{21})^2} \quad \text{(A32)}$$

$$AUMC_m^p = \frac{Dose^p \cdot CL_{12} \cdot (V_{ss}^p \cdot CL_{22} + V_{ss}^m \cdot CL_{11})}{(CL_{11} \cdot CL_{22} - CL_{12} \cdot CL_{21})^2} \quad \text{(A33)}$$

$$AUMC_p^m = \frac{Dose^m \cdot CL_{21} \cdot (V_{ss}^p \cdot CL_{22} + V_{ss}^m \cdot CL_{11})}{(CL_{11} \cdot CL_{22} - CL_{12} \cdot CL_{21})^2} \quad \text{(A34)}$$

$$AUMC_m^m = \frac{Dose^m \cdot (V_{ss}^p \cdot CL_{12} \cdot CL_{21} + V_{ss}^m \cdot CL_{11}^2)}{(CL_{11} \cdot CL_{22} - CL_{12} \cdot CL_{21})^2} \quad \text{(A35)}$$

Dividing Eqs. (A32)–(A35) by Eqs. (13)–(16) for the AUC values and substituting Eqs. (5) and (8) for MRT as well as Eq. 28 for EE into the results yields Eqs. (25)–(27) for the AUMC/AUC ratios.

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NOMENCLATURE

$—^p$, $—^m$	Administered parent drug (p) or metabolite (m)
$—_p$, $—_m$	Measured parent drug (p) or metabolite (m)
AUC	Area under the plasma concentration-versus-time curve
AUMC	Area under the moment curve (integral of t · c vs t)
B	Matrix of rate constants [Eq. (A1)]
B	Determinant of matrix B
B_{ij}	Adjoints of minor matrices of B
C	Plasma compartment concentration
C_T	Tissue compartment concentration
CL_d	Distribution clearance
CL_{12}	Conversion clearance of parent drug to metabolite
CL_{21}	Conversion clearance of metabolite to parent drug

CL_{10}	Sum of all elimination clearance processes operating on parent drug except CL_{12}
CL_{20}	Sum of all elimination clearance processes operating on metabolite except CL_{21}
CL_{11}	Summary clearance: $CL_{10} + CL_{12}$
CL_{22}	Summary clearance: $CL_{20} + CL_{21}$
Dose	Dose of compound administered
EE	Exposure enhancement
k_{ij}	Rate constant, compartment i to j (see Fig. 1)
k_1	Summary rate constant, $k_{10} + k_{12} + k_{13}$
k_2	Summary rate constant, $k_{20} + k_{21} + k_{24}$
MRT	Mean residence time of compound in body
MRTc	Mean residence time of compound in central compartment
t	Time
Vc	Volume of central compartment
V_T	Volume of tissue compartment
V_{ss}	Steady-state volume of distribution

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