A Novel Extravascular Input Function for the Assessment of Drug Absorption in Bioavailability Studies

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Purpose. Flexible parametric models describing the input process after extravascular drug administration are needed for the assessment of absorption rate and the use of population methods in bioavailability and bioequivalence studies.

Methods. The oral concentration-time curve modeled as the product of the input and disposition function in the Laplace domain was obtained by numerical inversion methods for parameter estimation. The utility of the inverse Gaussian input density was examined using bioavailability data of an extended-release dosage form. Measures of rate of absorption and the cumulative absorbed amount profile were defined in terms of the estimated model parameters.

Results. Accurate estimation of absorption parameters was achieved by simultaneous fitting of the extravascular and intravascular data (describing the latter by a triexponential function). The new input function allowed a direct estimation of both extent of absorption and mean absorption time.

Conclusions. The findings suggest that the inverse Gaussian density is a useful input function. Its flexibility may reduce the effect of model misspecification in parameter estimation. All parameters can be readily interpreted in terms of the absorption process.

KEY WORDS: pharmacokinetics; input model; bioavailability; absorption rate; extended release.

INTRODUCTION

The oral route is the most common and convenient drug delivery approach. However, in contrast to the well established theoretical framework for the analysis of drug disposition curves a comparable parametric modeling concept is not available for the evaluation of drug absorption after oral application. First, there is a lack of flexible parametric models which can be used to describe the complex process of drug input into the disposition system. Second, since the input and disposition model determine the resulting oral concentration-time profile by a convolution operation it is often impossible to calculate an analytical function for the oral curve. (An exception is the simplest case characterized by monoexponential input and disposition functions which lead to the well-known Bateman function.) Hence data analysis is usually limited to the analysis of curve moments by numerical integration (i.e., the area under the curves, *AUC* and *AUMC*, as the zeroth and first moments, respectively) instead of estimating model parameters by non-linear regression. Using the moment method one can calculate bioavailability F and mean absorption time *MAT*. However, disadvantages of this type of conventional data analysis are that the time profile of the absorption rate (or the cumulative absorbed amount) is not available and the parameter *MAT* is obtained as difference of two residence times which limits the reliability of its estimation. Furthermore, without analytical curve model it is impossible to predict concentration time-profiles following multiple dosing or to apply population models for parameter estimation. In principle this also holds for deconvolution methods with the help of which one can obtain the time course of drug absorption rate but no parametric model of the oral concentration-time profile. Another drawback of this nonparametric approach is its numerical instability.

The proper modeling of drug input is of particular importance for the evaluation of extended-release dosage forms. Thereby, the slow input process may mask parts of the distribution process in the body. The resulting problem of model identifiability is of fundamental nature and can only be overcome by an independent assessment of drug disposition, as done in the traditional approach of bioavailability determination (two-period crossover design).

In this paper we introduce a parametric method which is essentially different from the deconvolution approach or numerical methods which represent special cases of the latter, like the methods of Wagner-Nelson and Loo-Riegelmann. Based on the application of the theory of residence time distributions (1–3) the kinetic process after oral application is divided into two crucial steps described by the input transit time density and the disposition residence time density, respectively. The inverse Gaussian density function is chosen as a flexible input function. The convolution problem involved in modeling the oral concentration-time profile is circumvented by formulating the model in the Laplace domain and applying numerical inverse Laplace transformation in fitting the model to the data. The objective was to work out the advantages of the inverse Gaussian density as an input function for a sustained-release dosage form and to illustrate its utility by application to a real-data example.

METHODS

Pharmacokinetic Model

The plasma drug concentration-time curve observed after oral drug administration is the result of the (independent) action of the input process (absorption) and the output process (disposition). Thus, the pharmacokinetic system consists of two subsystems, the input system (release and absorption kinetics) and the disposition system (kinetics after intravenous drug administration) characterized by the input transit time density function f_A and the disposition residence time density f_D, respectively (Figure 1). (In accordance with conventional nomenclature we use the term "absorption" for "input".) If the subsystems can be arranged in series, then the random residence times are additive under the assumption that the processes are independent of each other [e.g., (4)]. The most general model for monotone decreasing disposition curves is a sum of exponentials (1),

$$C_{iv}(t) = \sum_{i=1}^{n} A_i e^{-\lambda_i t} \qquad (1)$$

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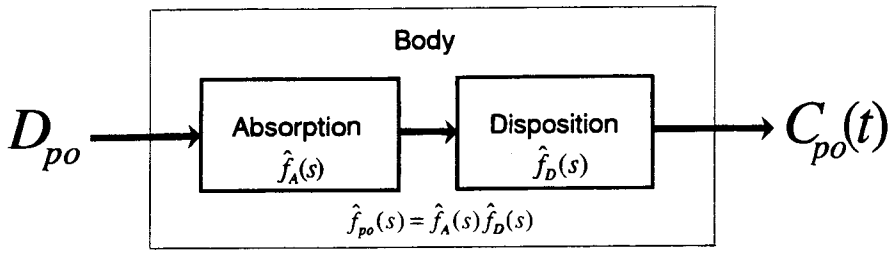

Fig. 1. The input (absorption) and disposition process as consecutive subsystems determining the response of the system to extravascular drug administration [Eqs. (1)–(7)].

where $C_{iv}(t)$ denotes the concentration-time profile after an intravenous dose D_{iv}. The corresponding density function of disposition residence times is given by

$$f_D(t) = \frac{C_{iv}(t)}{AUC} = \frac{C_{iv}(t)}{D_{iv}/CL} = \sum_{i=1}^{n} \alpha_i \lambda_i e^{-\lambda_i t}, \qquad \sum_{i=1}^{n} \alpha_i = 1 \tag{2}$$

As in previous applications to pharmacokinetic transit time processes (5) we use the inverse Gaussian distribution as a model of the input time distribution. The choice of the inverse Gaussian is made on the basis of its flexibility and appropriate asymptotic behavior, yet containing only few parameters which can be readily interpreted. Thus, while the underlying theory is the first passage time distribution of a random walk process (5,6), its role here is simply that of an empirical model. Denoting the mean input time or mean absorption time by MAT and the normalized variance of the distribution by CV_A^2 the inverse Gaussian density is given by (6)

$$f_A(t) = F\sqrt{\frac{MAT}{2\pi CV_A^2 t^3}} \exp\left[-\frac{(t - MAT)^2}{2CV_A^2 MAT t}\right] \tag{3}$$

The factor $F(<1)$ which represents bioavailability accounts for the fact that $f_A(t)$ [Eq. (3)] is the density of a defective distribution F_A

$$F_A(\infty) = \int_0^\infty f_A(t)\, dt = F < 1 \tag{4}$$

Let $\hat{f}(s)$ denote the Laplace transform of a function $f(t)$, i.e., $\hat{f}(s) = \int_0^\infty e^{-ts} f(t)\, dt$. The residence time density of the complete model f_{po} (Figure 1) can explicitly be written in the Laplace domain as a product of the subsystem densities

$$\hat{f}_{po}(s) = \hat{f}_A(s)\hat{f}_D(s) \tag{5}$$

Substituting the Laplace transform of Eqs. (2) and (3) into Eq. (5) gives

$$\hat{f}_{po}(s) = F \exp\left\{\frac{1}{CV_A^2} - \left[\frac{MAT}{CV_A^2/2}\left(s + \frac{1}{2MATCV_A^2}\right)\right]^{1/2}\right\} \times \sum_{i=1}^{n} \frac{\alpha_i \lambda_i}{s + \lambda_i} \tag{6}$$

and we obtain the following equation for the Laplace transform $\hat{C}_{po}(t)$ of the oral concentration-time curve $C_{po}(t)$ after an oral dose D_{po} assuming that the intravenous reference curve [Eq. (1)] has been measured after a dose D_{iv}:

$$\hat{C}_{po}(s) = F\frac{D_{po}}{D_{iv}} \exp\left\{\frac{1}{CV_A^2} - \left[\frac{MAT}{CV_A^2/2}\left(s + \frac{1}{2MATCV_A^2}\right)\right]^{1/2}\right\} \times \sum_{i=1}^{n} \frac{A_i}{s + \lambda_i} \tag{7}$$

Numerical inverse Laplace transformation has to be applied to convert Eq. (7) into the time domain, i.e., to calculate $C_{po}(t)$.

Cumulative Absorbed Amount

Having estimated the parameters of the input model F, MAT and CV_A^2, one can calculate the rate of absorption versus time curve using Eq. (3). While the rate is proportional to the input time density function [Eq. (3)], the time course of the fraction absorbed is given by [cf. Eq. (4)]

$$F_A(t) = \int_0^t f_A(\tau)\, d\tau \tag{8}$$

The cumulative inverse Gaussian distribution $F_A(t)$ can be expressed in terms of the standard normal distribution Φ (6)

$$F_A(t) = \Phi\left[\sqrt{\frac{MAT}{CV_A^2 t}}\left(\frac{t}{MAT} - 1\right)\right] + e^{2/CV_A^2}\Phi\left[-\sqrt{\frac{MAT}{CV_A^2 t}}\left(\frac{t}{MAT} + 1\right)\right] \tag{9}$$

The fact that the function Φ is available in parameter estimation and computer algebra software facilitates the use of the absorption profile $F_A(t)$ [Eq. (9)] in practice.

Measures of Rate of Absorption

In order to reduce the information on the rate of absorption contained in $f_A(t)$ [or $F_A(t)$] to a single measure we can calculate $t_{A,max}$, the time at which the input rate attains its maximum value [mode of the inverse Gaussian (6)]

$$t_{A,max} = MAT\left[\sqrt{1 + \frac{9}{4}CV_A^4} - \frac{3}{2}CV_A^2\right] \tag{10}$$

The measure $t_{A,max}$ increases proportionally to *MAT*, i.e., the ratio $t_{A,max}/MAT$ is only dependent on the relative dispersion of absorption times CV_A^2. The median absorption time $t_{0.5}$ which is obtained by solving the equation

$$F_A(t_{0.5}) = \frac{1}{2} \tag{11}$$

has been proposed as an appropriate measure of absorption rate in the case of skewed input densities (7). Alternatively, the total absorption time can be characterized by the time $t_{0.9}$ at which 90% of the available dose is absorbed, which analogous to Eq. (11) is implicitly given by $F_A(t_{0.9}) = 0.9$.

Note that both the mean absorption time *MAT* and the mean disposition residence time, $MDRT = AUMC_{iv}/AUC_{iv}$, are model independent terms which determine the mean residence time of drug in the body after oral administration, *MBRT* [e.g., (2,3)]:

$$MBRT = \frac{AUMC_{po}}{AUC_{po}} = MAT + MDRT \tag{12}$$

Simulations

The effect of the mean and the relative dispersion of absorption time distributions (*MAT* and CV_A^2) on absorption profiles has been simulated using MAPLE V (Waterloo Maple Software, Waterloo, Ont., Canada) and Eqs. (3) and (9) (Figure 2). Note that the *MAT* characterizes the input rate and is a scale parameter, whereas CV_A^2 acts as a shape parameter of the curves. Table I summarizes derived measures of absorption rate. The CV_A^2 values in Table I were chosen to illustrate the dependency of the various absorption rate metrics on the relative dispersion of absorption times in a range representative for slow release formulations. As indicated in Table I for all metrics and in Figure 2 for the time $t_{0.9}$ at which 90% of the totally available amount is absorbed (i.e., 0.9 FD_{po}) the parameter CV_A^2 has only a minor influence on the rate of absorption normalized by *MAT*. It can be concluded that after 2 *MAT* about 90% of the available dose has been absorbed and that the median absorption time is about 0.75 *MAT*. Note that $t_{A,max}$ follows directly from Eq. (10) while the parameters $t_{0.5}$ and $t_{0.9}$ have been calculated by solving Eq. (11) [after substituting Eq. (9)] using MAPLE [for $t_{0.9}$ the value 1/2 in Eq. (11) has been replaced by 0.9].

Parameter Estimation

Parameter estimation by non-linear regression is applied in combination with inverse Laplace transform to obtain $C_{po}(t)$ from $\hat{C}_{po}(s)$[Eq. (7)]. This can be performed by numerical inversion methods implemented in various curve fitting software, as for example, SCIENTIST (MicroMath Scientific Software, Salt Lake City, USA) for DOS and MINIM (8) for Macintosh computers. The method is now also available for the widely used ADAPT II program (Schalla and Weiss, in preparation).

It is obvious from Eq. (7) that the disposition parameters A_i and λ_i ($i = 1 \cdots n$) are an integral part of the curve model. There are two ways to overcome the inherent difficulties in identifying the disposition system from oral concentration-time data: First, after initially fitting the $C_{iv}(t)$-curve [Eq. (1)] the estimated parameters [A_i and λ_i ($i = 1 \cdots n$)] are substituted as fixed parameters into Eq. (7) in order to estimate *F*, *MAT* and CV_A^2, or second, both Eqs. (1) and (7) are simultaneously fitted to the $C_{iv}(t)$ and $C_{po}(t)$ data. We used the latter method in an attempt to smooth the effect of interoccasion variability of the disposition parameters on parameter estimation.

APPLICATION

The method is applied to data of an oral extended-release product investigated together with an intravenous reference in a bioavailability study. The product is disguised for confidentiality and the results are presented merely for illustration of the method. The data from 8 subjects with 16 and 24 plasma concentrations collected between 5 minutes and 32 hours after oral and intravenous administration, respectively, were analyzed. Starting with a separate fit of the intravenous data [whereby a triexponential decline, i.e., $n = 3$ in Eq. (1), was found appropriate], the intravenous and oral data of each subject are fitted simultaneously using Eqs. (1) and (7), respectively, utilizing the numerical inverse Laplace transformation provided by SCIENTIST. Thereby, the results of the initial separate fit of the intravenous data were used as starting values. The individual parameter estimates of the absorption model together with their coefficients of variation are given in Table II. The goodness of fit is indicated by values of r^2 around 0.9; the reliability of parameter estimation is also reflected by the relatively low standard deviations of the individual estimates (which are—except Subj. 5—for *F* and *MAT* in the order of 10% or less) and the lack of significant correlation among the estimates of different parameters. The disposition parameter which is of special interest in the present context is the mean disposition residence time *MDRT* since together with *MAT* it determines the total residence time in the body after oral administration. [Eq. (12)]. The *MDRT* values shown in Table II were calculated from A_i and λ_i ($i = 1, 2, 3$) using the standard equation [e.g., (3)]. Figure 3 shows two examples of the curve fits, representing the data sets with the best (Subj. 7) and worst fit (Subj. 4) according to total sum of squared deviations of the simultaneous fit to the i.v. and oral data. Also shown in Figure 3 are the corresponding input rate profiles $D_{po}f_A(t)$ predicted by Eq. (3).

Comparison with Other Parametric Approaches

The principle problem with fitting parametric models to extravascular data is to apply suitable models for both the input and the disposition process. The effects of corresponding model misspecifications are illustrated in Figures 4 and 5 using the data of Subj. 8. First, the consequences of an inadequate input model are shown by the best fit obtained with a first order absorption model (as the simplest input model)

$$f_A(t) = F\lambda_A e^{-\lambda_A t} \tag{13}$$

and the "correct" disposition model [Eq. (1), $n = 3$]. The poor fit in Figure 4 shows the failure of the exponential density for an extended-release dosage form. This is not surprising since Eq. (13) does not account for the delayed increase in input rate [Eq. (3)] reaching its maximum after about 1.7 ± 0.5 hr. The resulting biases in *F* and $MAT = 1/\lambda_A$ (compared to the estimates in Table II) are −7.8 and +22%, respectively. Note that an exponential distribution [Eq. (13)] is characterized by $CV_A^2 = 1$, which corresponds to a bias of +31%. Second, an appropriate input function [Eq. (3)] is combined with an inadequate

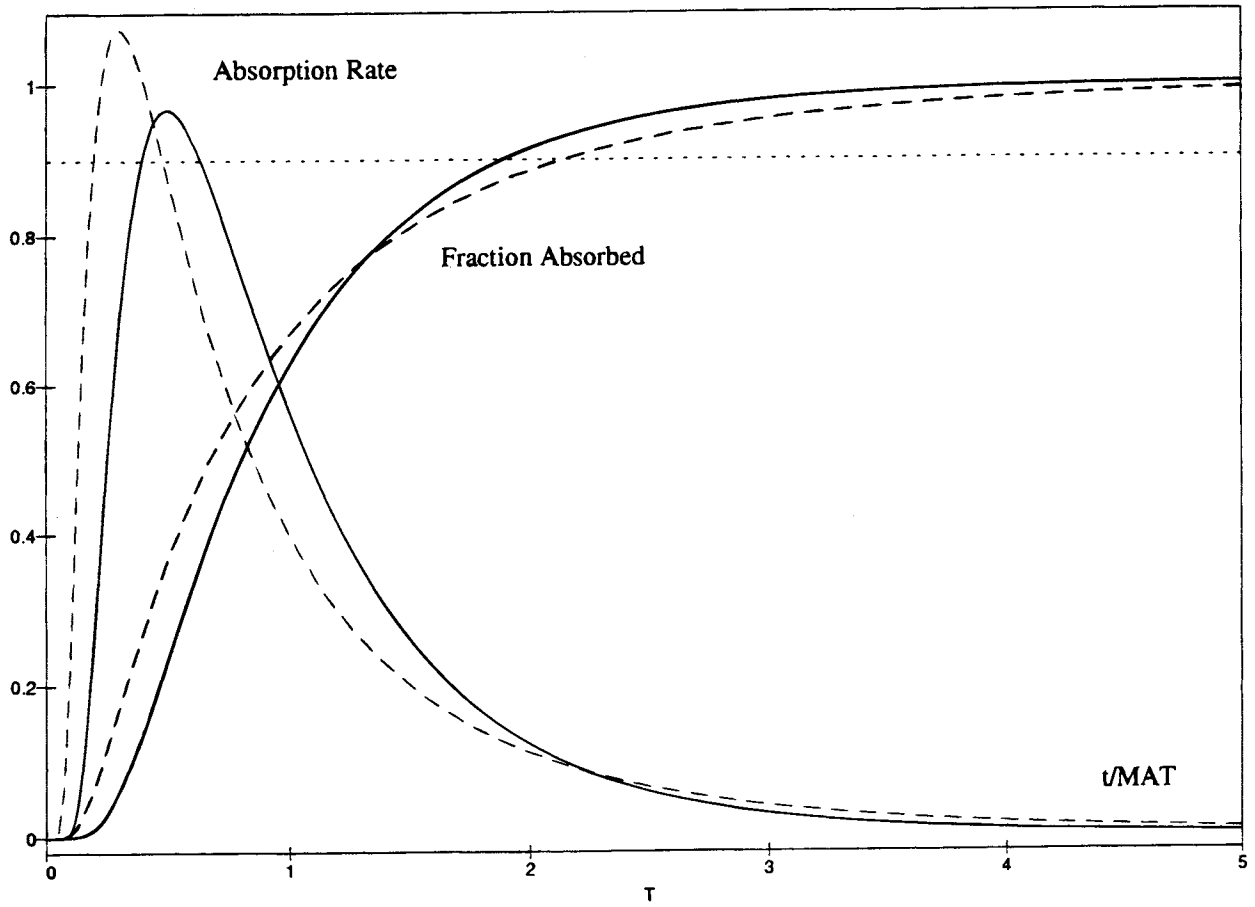

Fig. 2. Time course of the absorption rate and fraction absorbed simulated as function of normalized time ($T = t/MAT$) using Eqs. (3) and (9), respectively (solid line $CV_A^2 = 0.5$, dashed line $CV_A^2 = 1.0$). Note that the cumulative amount absorbed profile crosses the short-dashed line at $t_{0.9}/MAT$.

disposition model. A one-compartment disposition model, for example, is wrong *a priori*, since the underlying assumption of instantaneous distribution in the whole body is only a crude oversimplification. Here a visual inspection of the fit obtained after substituting in Eq. (7) the triexponential by a monoexponential function does not reveal the problem since the curve fit remains nearly unchanged (Figure 5). This structural misspecification of the disposition model leads to biases in *MAT* and CV_A^2 estimates of −2% and −48%, respectively. However, the most striking drawback lies in the fact that in this case the parameter *F* cannot be estimated directly.

Table I. Relations Between Relative Dispersion of Absorption Times, CV_A^2, and Normalized Measures of Absorption Rate, $t_{0.9}$, $t_{0.5}$, and $t_{A,max}$, Normalized by the Mean Absorption Time, *MAT*

CV_A^2	$t_{0.9}/MAT$	$t_{0.5}/MAT$	$t_{A,max}/MAT$
0.4	1.81	0.84	0.57
0.5	1.89	0.80	0.50
0.6	1.95	0.77	0.45
0.7	2.01	0.75	0.40
0.8	2.06	0.72	0.36
0.9	2.10	0.70	0.33
1.0	2.14	0.68	0.30
1.1	2.18	0.66	0.28
1.2	2.21	0.64	0.26

DISCUSSION

The real data example suggests that the inverse Gaussian distribution is a flexible empirical input model for an extended-release dosage form. An important advantage of the new model is that all parameters can be estimated directly and that they have a definite meaning in terms of the absorption process: *F* characterizes the fraction of drug absorbed, *MAT* the rate of absorption and CV_A^2 the shape of the absorption profile. Based on these parameters one can calculate temporal extents of the input rate (as $t_{A,max}$, $t_{0.5}$ and $t_{0.9}$) and/or predict the time courses of the cumulative absorbed amount and of the rate of absorption.

The role of the parameters *MAT*, CV_A^2 and the ratio *MAT/MDRT* in determining log-concave concentration-time profiles which are typical for sustained-release products has been discussed previously (2). The log-concavity of the oral concentration-time profiles in the real data example is in accordance with the prediction by the *MAT/MDRT* criterion: A mean ratio of *MAT/MDRT* = 0.98 ± 0.43 as obtained from the values in Table II is suggestive for generating log-concave curves (2).

Table II. Estimates of F, MAT, and CV_A^2 and Calculated Values of $t_{A,max}$ and $MDRT$ (the latter was calculated from the parameters of a triexponential disposition function). The Goodness of Fit is Indicated by the r-squared Criterion

Subj No.	F, %	MAT, min	CV_A^2	$t_{A,max}$, min	r_{po}^2	$MDRT$, min	r_{iv}^2
1	63.0	254.5	1.015	76.1	0.971	309.7	0.995
	(3.6)	(21.6)	(0.094)				
2	56.9	186.6	0.492	94.2	0.960	335.8	0.996
	(3.8)	(20.9)	(0.097)				
3	66.4	258.7	0.521	126.2	0.946	323.2	0.994
	(6.0)	(33.6)	(0.106)				
4	62.4	396.0	0.696	159.1	0.912	283.8	0.991
	(9.3)	(34.5)	(0.065)				
5	69.4	217.4	0.754	82.3	0.989	211.0	0.947
	(23.5)	(85.5)	(0.570)				
6	77.4	336.0	0.756	127.0	0.962	296.5	0.995
	(4.7)	(20.6)	(0.067)				
7	58.8	319.8	1.243	80.3	0.973	258.1	0.995
	(2.9)	(24.1)	(0.131)				
8	60.5	196.7	0.766	73.6	0.973	319.8	0.999
	(3.6)	(17.0)	(0.096)				
Mean	64.4	270.7	0.780	102.4		292.2	
SD	6.6	73.8	0.247	31.3		41.0	

Note: Values in parenthesis represent precision of parameter estimate (p) expressed as approximate standard deviation SD(p).

However, it should be noted that both empirical functions, which have been proposed as minimal models for log-concave curves, the biexponential function (Bateman function) and unimodal gamma curves (2, 5, 9), completely failed to describe the data.

Based on the assumption that for slowly releasing preparations dissolution is the rate-controlling step of the input process one can infer that MAT differs from the *in vitro* dissolution rate $MDT_{\text{in vitro}}$ by a time scaling factor (10) while the shape parameter CV_A^2 may reflect the relative dispersion of the *in vitro* dissolution time distribution. Thus the parameterization in terms of MAT and CV_A^2 may offer new possibilities in establishing quantitative correlation of *in vitro* dissolution profiles with *in vivo* absorption data. Further, Eq. (9) appears of considerable utility in the analysis of *in vitro* dissolution data.

Although well established in bioavailability assessment it should be reemphasized that the knowledge of the disposition function is a *conditio sine qua non* for any modeling of input processes (2, 11, 12). If, for example, the test of new flexible input functions is based on a wrong disposition function (13,14)—and a monoexponential disposition function is *a priori* wrong—false conclusions may be drawn from the fact that an excellent fit is achieved. This is clear from the above considerations and is also demonstrated in Figure 5 where a reasonable fit was obtained using a monoexponential disposition curve on the cost of erroneous estimates of the absorption parameters. On the other hand, the potential misspecification of the absorption model due to within-subject interoccasion variability in disposition may unavoidably lead to biased absorption parameters (12). However, it is obvious that the effect of "interoccasion model misspecification" (12) can be minimized by avoiding any *a priori* structural misspecification of the absorption and/or disposition model.

The present model can be easily extended to a situation where the release rate is not the rate limiting step of the absorption process (15). Assuming that the release time distribution is inverse Gamma distributed (e.g., based on *in vitro* results) and the absorption process is first order (with rate constant k) then $\hat{f}_A(s)$ in Eq. (5) has to be replaced by

$$\hat{f}_A(s) = \frac{k}{s + k}\hat{f}_{IG}(s) \tag{14}$$

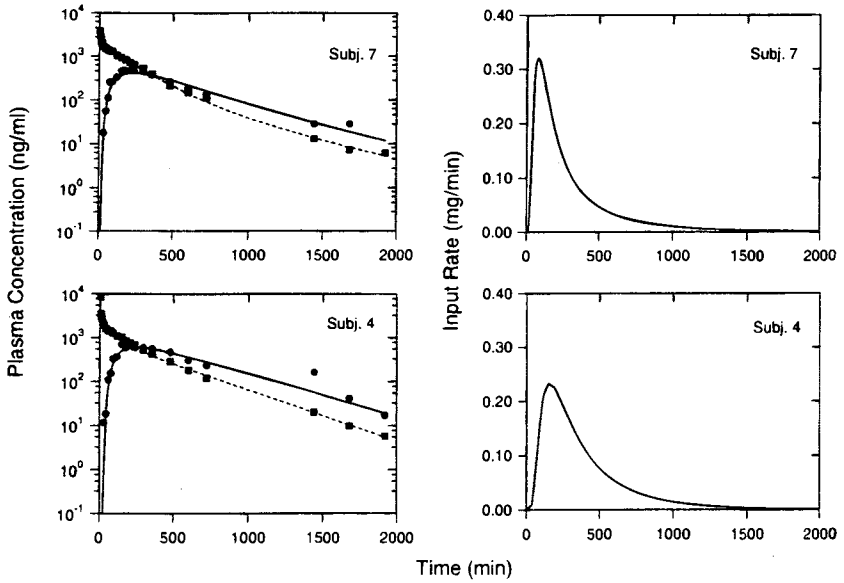

Fig. 3. Plot of C_{po} (●) and C_{iv} (■) versus time data for Subj. 6 (best fit) and Sub. 3 (worst fit), together with the fitted curves and the corresponding input rate functions [Eq. (3)]. The simultaneously fitted curves for C_{po} are shown as solid lines, and those for C_{iv} as dashed lines.

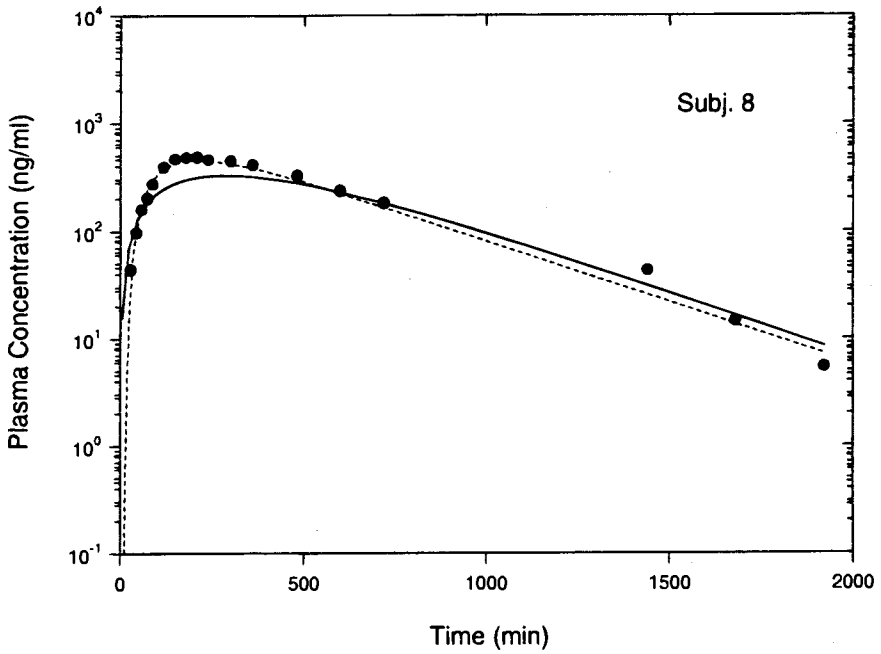

Fig. 4. Plot of the oral data (Subj. 8) and the fitted response (solid line) after structural model misspecification of the input model: the inverse Gaussian density is substituted by a monoexponential input function. The fitted curve for the "correct" model [Eq. (7)] is shown as dashed line.

where $\hat{f}_{IG}(s)$ is Laplace transform of the inverse Gaussian distribution. Alternatively, the response to an oral solution $C_{soln}(t)$ could serve as reference curve if $C_{soln}(t)$ and/or $\hat{C}_{soln}(s)$ can be described by an analytical function.

The most appealing aspect of the present method is its potential utility in the evaluation of bioavailability data. The results also indicate that the measures $t_{A,max}$, $t_{0.5}$ and $t_{0.9}$ may prove useful for assessment of rate of absorption in bioequiva-

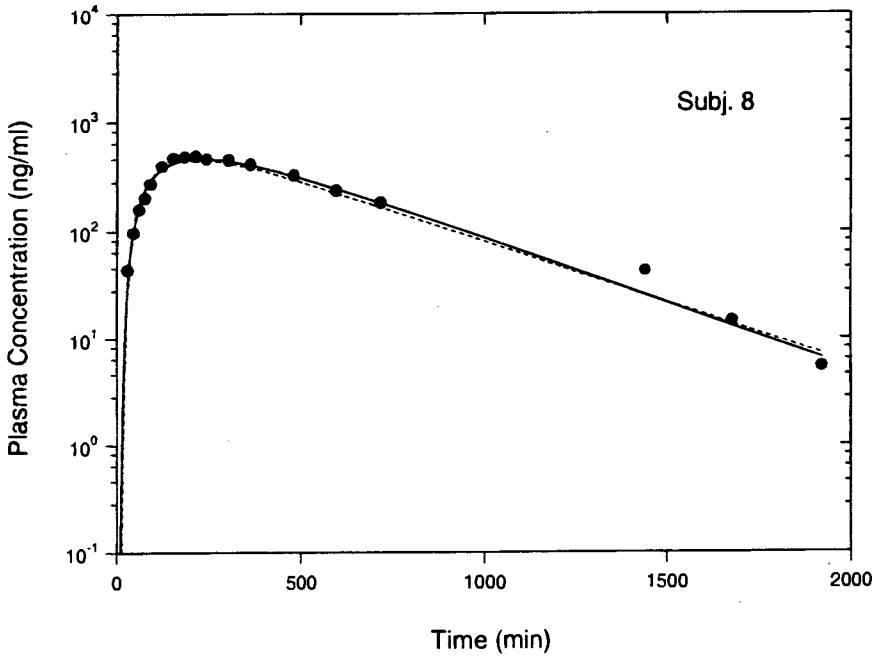

Fig. 5. Plot of the oral data (Subj. 8) and the fitted response (solid line) after structural model misspecification of the disposition model: the triexponential function is substituted by a monoexponential disposition function. The fitted curve for the "correct" model [Eq. (7)] is shown as dashed line.

lence studies where the question of a suitable rate metrics is still open [e.g., (16–18)]. It is important to note that contrary to previous attempts in the literature such an interpretation of *MAT* in terms of temporal extents of drug absorption is impossible if *MAT* is estimated nonparametrically on the basis of Eq. (12) using numerical integration methods. Although the discussion of deconvolution methods is out of the scope of the present paper, it should be noted that it is still unclear whether the ill-posed nature of the underlying inverse problem can be overcome by more advanced methods like the maximum entropy method (19). Furthermore, the deconvolution approach itself does not deliver any measure characterizing the absorption process. Although the calculated absorption rate profile could be subsequently fitted by Eq. (3) this would offer no advantage in comparison to the present method which additionally provides a parametric model of the oral concentration-time profile. In this sense also the nonparametric (spline function based) population method for deconvolution (20) cannot be regarded as a direct alternative.

In view of the practical importance of bioavailability and bioequivalence considerations it is an advantage of the present method that the absorption parameters can be directly estimated and readily interpreted. Furthermore, a parametric input model allows the use of mixed effects modeling (12, 21, 22) and the prediction of the time courses of drug concentration after multiple oral dosing. Because of their independence of a specific structural model, the measures F, MAT, and CV_A^2 can, in principle, also be calculated using the method of statistical moments and may be useful for the investigation of *in vitro—in vivo* correlations of drug dissolution. It should also be noted that the interest in the quantification of the absorption characteristics of pharmaceutical dosage forms has been generated not only in the evaluation of oral bioavailability and bioequivalence studies—in academia, pharmaceutical industry or regulatory agencies—but more recently also in the development of alternative routes of drug delivery to the body (e.g., transdermal, intradermal, buccal). Although the absorption kinetics of the investigated extended-release formulation is well characterized by inverse Gaussian density these results cannot be generalized and further applications are necessary to examine its utility as an empirical model of the absorption process.

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