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Calculation of partial components of bioavailability in slow release formulations using model-independent methods

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Abstract

In certain slow release formulations the total dose of drug is subdivided into at least two fractions with different release capacities; these may display different degrees of bioavailability. In this type of formulation, calculation of the amount of biavailability by conventional methods does not permit one to differentiate the contribution of the different dose fractions to the total bioavailability of the formulation. This paper develops a model-independent method that permits optimization of the different components of bioavailability regarding amount and rate, combining convolution/deconvolution methods as well as non-linear regression. The method calculates bioavailability parameters by optimization of a prescribed input function in the form of a Laplace transform using the MULTI(FILT) program. The serum level curve after the administration of a slow release formulation is used as a response function obtained by convolution between a prescribed input function and a weighting function expressed as a polyexponential. The method was tested using simulated serum level data with added random error. In all cases the bioavailability parameters were calculated with good precision.

Keywords: Slow release formulation; Bioavailability; Model-independent method

1. Introduction

In certain slow release formulations the total dose of drug incorporated in the formulation is found subdivided into at least two fractions with different release capacities that can have different degrees of bioavailability. One of these fractions shows rapid dissolution, allowing therapeutic drug levels to be reached rapidly, while the other fractions display controlled dissolution and are responsible for attaining sustained drug levels in the blood. Calculation of the amount of bioavailability in this type of formulation with conventional methods does not permit one to differentiate the contributions of the different fractions of the dose in the overall bioavailability of the formulation.

The aim of the present work was to analyze algebraically and numerically the methods of convolution/deconvolution combined with non-linear regression methods in the characterization of partial components of bioavailability in this kind of slow release formulation.

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2. Methods

2.1. Theoretical considerations

In linear systems, the convolution operation calculates response functions $R(t)$ using input $I(t)$ and weighting functions $W(t)$ and is algebraically defined using the convolution integral:

$$R(t) = \int_0^t I(t) \cdot W(t-\tau)\mathrm{d}t \quad (1)$$

or

$$R(t) = I(t) \cdot W(t) \quad (2)$$

The convolution operation and its inverse, deconvolution, can be accomplished algebraically using Laplace transforms (Rescigno and Segre, 1965). According to this procedure, Laplace transforms of response $R(s)$, input $I(s)$ and weighting $W(s)$ functions can be expressed as:

$$R(s) = L[R(t)] \quad (3)$$

$$I(s) = L[I(t)] \quad (4)$$

$$W(s) = L[W(t)] \quad (5)$$

The convolution operation corresponding to Eq. 1 can be expressed using the functions transformed as:

$$R(s) = I(s) \cdot W(s) \quad (6)$$

Consequently, the deconvolution operation to obtain the input function $I(t)$ can be solved algebraically as a quotient using the transformed functions, thus:

$$I(s) = R(s)/W(s) \quad (7)$$

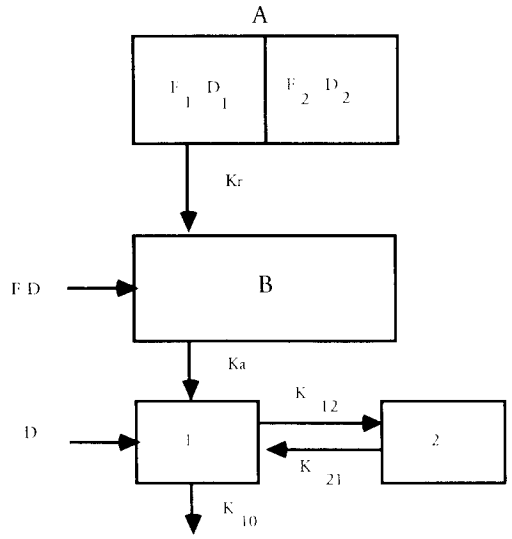

Fig. 1. Two-compartment pharmacokinetic model with first-order release and absorption. The intravenous dose (D) is incorporated into compartment 1; the dose of the solution (FD) is incorporated into compartment B (absorption compartment); the slow release formulation with a sustained release component (F_1D_1) and an instantaneous release component (F_2D_2) are represented by compartment A.

In practice, the input function for different conditions of administration can be solved easily using Laplace transforms.

Fig. 1 shows the kinetic behaviour of a hypothetical drug whose disposition processes correspond to a two-compartment model administered: (A) by single i.v. injection of a prescribed dose (D); (B) by the extravascular route in the form of solution ($F \cdot D$), where F is the fraction

Table 1
Algebraical equations representing Laplace transforms of input functions obtained by deconvolution in slow release formulations

Weighting function	Response function	Input function	Laplace transforms of input function
i.v. bolus	solution	absorption (rate and amount)	$FD \cdot K_a/(s+K_a)$
i.v. bolus	slow release	release, absorption and amount	$F_1 \cdot D_1 \cdot K_a K_r/(s+K_a)(s+K_r)$
Solution	slow release	release and amount	$F_1 D_1 K_r/(s+K_r)$
Solution	slow release + instantaneous release	release and amount	$(F_1 D_1 K_r/(s+K_r)) + F_2 D_2$
i.v. bolus	slow release + instantaneous release	release, absorption and amount	$\frac{F_1 D_1 \cdot K_r K_a}{(s+K_r)(s+K_a)} + \frac{F_2 D_2 K_a}{(s+K_a)}$

of bioavailability; and (C) by the extravascular route as a slow-release formulation (SRF) that includes a component of slow release (F_1D_1) with first-order dissolution and absorption and an instantaneous release component (F_2D_2) with first-order absorption, where F_1 and F_2 are the fractions of bioavailability which correspond to the slow and instantaneous release components, respectively.

Taking into account that the system defined in Fig. 1 can be considered as linear, we can write algebraically the deconvolution among the different time functions to characterize the different kinds of input functions, shown in Table 1.

These input functions contain information about the different components of bioavailability in both amount and rate and it may be optimized using numerical methods.

This paper develops a method that permits optimization of the different components of bioavailability regarding the amount and rate by an input function combining convolution/deconvolution methods as well as non-linear regression.

2.2. Study with simulated data

In order to validate the proposed method, a study was performed with simulated data using 0%, ±5 and ±10% of added random error generated from the model in Fig. 1 and using the following parameters: $K_r = 0.1\ h^{-1}$; $K_a = 1\ h^{-1}$; $\alpha = 5\ h^{-1}$; $\beta = 0.3\ h^{-1}$; $V_c = 5$ l; where K_r is the first-order release constant, K_a denotes the first-order absorption constant, α and β are first-order hybrid rate constants corresponding to the two-compartment kinetic model and V_c represents the distribution volume of compartment 1.

The sampling schedule used to predict serum concentrations was the following:

(i.v.)	0.25, 0.5, 0.75, 1.0, 1.5, 2, 3, 4, 6, 8, 10, 12 h;
(extravascular solution)	0.025, 0.05, 0.075, 0.1, 0.25, 0.5, 0.75, 1.0, 1.5, 2, 3, 4, 6, 8, 10, 12 h;
(SRF)	0.025, 0.05, 0.075, 0.1, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24, 36 and 48 h.

Calculations of the different simulated serum level curves were carried out using the NONLIN program in simulation mode (Weiner, 1986).

When the serum level curves are known, the cumulative inputs corresponding to different routes of administration and dosage forms may be determined by deconvolution.

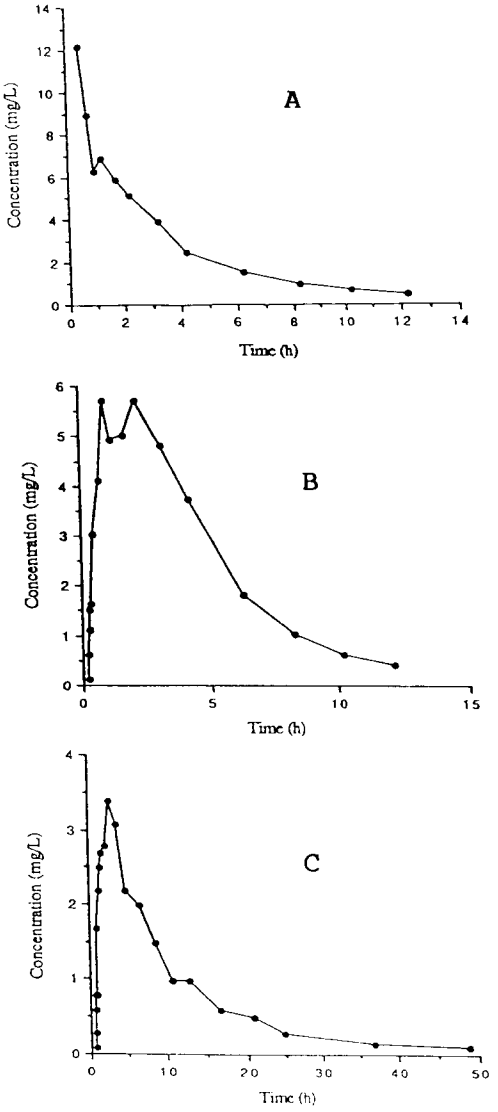

Fig. 2. Simulated serum levels (±10% random error) after administration by the following routes: (A) i.v. bolus-type, $D = 100$ mg; (B) extravascular aqueous solution, $D = 100$ mg; (C) extravascular SRF, $D_1 = 50$ mg, $D_2 = 50$ mg.

Numerical deconvolution of the simulated serum level curves was accomplished using a program of analytical deconvolution (Lanao et al., 1992). In this program, the response and weighting functions are fitted by a polyexponential equation and the deconvolution is performed using the method of Langenbucher and Möller (1983).

Optimization of the different components of bioavailability was accomplished with a non-linear regression program (MULTI(FILT)) (Yano et al., 1989; Yamaoka et al., 1991). This program carries out the curve fitting of concentration/time data by non-linear regression using Laplace-transformed equations corresponding to the weighting function expressed as polyexponential function convoluted with the input function characterized by the equations shown in Table 1. The bioavailability parameters in amount and rate included in the input function were considered parameters to be estimated by non-linear regression. The weighting function is assumed to be known in terms of polyexponential equation parameters. The response function optimized is taken in the form of experimental data pairs, representing the plasma concentration vs time.

3. Results

Fig. 2 shows the simulated serum levels ($\pm 10\%$ random error) after administration through the following routes: as an i.v. bolus-type injection; as an aqueous solution by the extravascular route, and as a slow release formulation (SRF) that includes slow and instantaneous release components. These serum level curves were fitted to a polyexponential by non-linear regression. The optimum number of exponentials corresponding to each curve as well as the coefficients and exponents of these equations are listed in Table 2.

From the polyexponential equations, cumulative inputs were obtained by analytical deconvolution corresponding to the following functions: (A) SRF (instantaneous + slow release)//i.v; (B) SRF (instantaneous + slow release)//extravascular solution. According to the results of the algebraic deconvolution, shown in Table 1, the cumulative inputs obtained by deconvolution contain information about the bioavailability of the sustained release formulation (SRF) in amount (F_1D_1 and F_2D_2) and rate (K_r and K_a) as shown in Fig. 3.

The use of strategies that combine convolution and non-linear regression by least squares permits the optimization of the different bioavailability parameters with sufficient precision and even calculation the bioavailability in amount corresponding to the instantaneous and slow doses separately.

Table 3 shows the bioavailability parameters in amount and rate for the SRF obtained by optimization of a prescribed input function applying non-linear regression with MULTI(FILT), using as a weighting function, in a model-independent way, the polyexponential equation previously ob-

Table 2
Polyexponential equations obtained by non-linear regression using simulated serum level data and different added random error

Route of administration	Random error (%)	F_1D_1	F_2D_2	n	A_1	λ_1	A_2	λ_2
i.v.	–	$D = 100$		2	8.02	0.30	12.15	5.07
	± 5%	$D = 100$		2	8.32	0.31	16.75	5.97
	± 10%	$D = 100$		2	8.53	0.32	22.50	6.73
Extravascular solution	–	$D = 100$		2	8.73	0.27	−8.73	2.36
	± 5%	$D = 100$		2	8.76	0.28	−8.76	2.34
	± 10%	$D = 100$		2	8.66	0.28	−8.66	2.34
Extravascular SRF	–	50	50	2	3.29	0.11	−3.29	3.05
	± 5%	50	50	2	3.34	0.11	−3.34	2.91
	± 10%	50	50	2	3.30	0.11	−3.30	2.90

n, optimum number of exponentials; A_i, coefficient of the exponential term; λ_i, exponent of the exponential term; F_1D_1, sustained release component; F_2D_2, instantaneous release component.

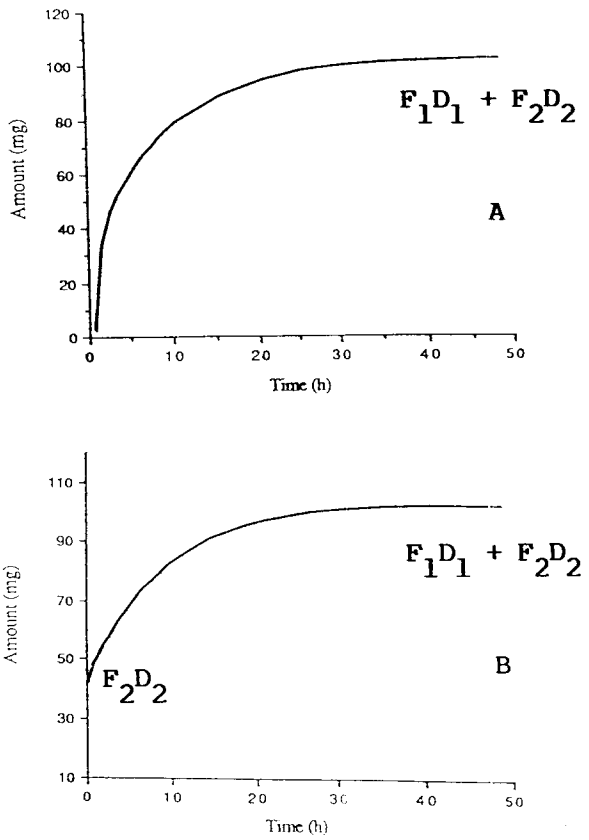

Fig. 3. Cumulative inputs obtained by analytical deconvolution from the polyexponential equations corresponding to the following functions (±10% random error): (A) SRF//i.v., SRF ($F_1D_1 = 50$ mg; $F_2D_2 = 50$ mg) – i.v. ($D = 100$ mg); (B) SRF//extravascular solution, SRF ($F_1D_1 = 50$ mg; $F_2D_2 = 50$ mg) – extravascular solution ($FD = 100$ mg).

tained from the simulated serum level curves after i.v. administration and administration as an extravascular solution. In all cases, the parameters optimized and, especially, the amount of bioavailability corresponding to the instantaneous and slow-release doses were calculated with good precision (variation coefficient less than 17%).

4. Discussion

The calculation of bioavailability becomes more complicated in certain slow release formulations, where the total dose of drug is divided in two fractions with different release profiles that may have different degrees of bioavailability. The use of model-dependent methods, such as compartmental models, in the calculation of bioavailability has severe limitations in this type of formulation, since flip-flop phenomena and model collapse may occur owing to the special kinetic profile of these formulations (Ronfeld and Benet, 1977). As may be seen in Fig. 2, extravascular administration of an oral solution of drug may lead, depending on the values taken by the pharmacokinetic parameters, to a collapse of the true pharmacokinetic model producing the phenomenon of vanishing exponential terms which has been described previously (Chan and Gibaldi, 1984,1985). In this simulation, the optimum number of exponentials obtained from the simulated data was two, which does not allow optimization of the model parameters shown in Fig. 1 using

Table 3
Bioavailability parameters (amount and rate) for the SRF calculated using MULTI(FILT) for different values of bioavailability in amount and rate

	Theoretical	No added error	CV (%)	Random error ± 5%	CV (%)	Random error ± 10%	CV (%)
F_1	1.00	1.02	(1.04)	1.13	(1.19)	1.09	(1.12)
F_2	1.00	0.98	(1.49)	0.96	(1.10)	0.96	(6.81)
Kr	0.10	0.10	(4.43)	0.11	(5.14)	0.17	(16.27)
F_1	0.75	0.77	(1.78)	0.76	(4.62)	0.82	(2.14)
F_2	1.00	0.99	(1.18)	1.00	(3.04)	0.98	(2.72)
Kr	0.10	0.10	(1.84)	0.09	(11.95)	0.10	(5.73)
F_1	0.50	0.51	(0.56)	0.50	(4.00)	0.65	(2.96)
F_2	1.00	0.99	(0.94)	1.00	(1.61)	1.00	(0.56)
Kr	0.10	0.10	(4.47)	0.10	(7.95)	0.17	(11.93)

Polyexponential equations corresponding to oral solution were used as weighting functions.

compartmental analysis and questions the use of model-dependent methods for estimating the bioavailability in amount and rate in this kind of formulations.

Traditionally, model-independent methods such as the area under the curve, statistical moments and numerical deconvolution have been used in calculating the bioavailability in different types of formulations. The main advantage is that these method avoid the assumptions of model-dependent methods, as happens with compartmental models.

The use of model-independent methods as numerical deconvolution permits one to estimate the total bioavailability of the formulation in amount from the maximum asymptotic value obtained in the cumulative input. The combined use of numerical convolution/deconvolution and non-linear regression proposed in the present work allows one to calculate, separately, the amount and rate of bioavailability of each of the components of the formulation with sufficient precision by optimizing the parameters of the input function.

The use of a program such as MULTI(FILT) facilitates the numerical solution of this type of problem. This program uses the fast inverse Laplace transform algorithm (FILT) which numerically generates the time course curve from the Laplace-transformed model equation corresponding to a prescribed input function as shown in Table 1, convoluted with a polyexponential equation corresponding to the weighting function. MULTI(FILT) is a non-linear regression analysis program where FILT is combined with a non-linear regression program (MULTI) that permits optimization by least squares of the parameters of the prescribed input function.

The advantages of the method can be summarized as follows:

(1) Since it is a model-independent method, it is not necessary to know the distribution and elimination kinetics of the drug or to use model-dependent analysis.
(2) It allows one to estimate the different components of bioavailability in amount and rate in this kind of formulation
(3) There is minimal mathematical complexity in its application.

The main limitations of the method would be:

(1) It is limited to linear systems.
(2) There may be difficulty in obtaining a sufficient number of data to be able to suitably estimate the kinetic profile of the drug after administration of the different formulations, especially in the case of sustained action formulations.
(3) Appropriate use must be made of the deconvolution and non-linear regression methods.

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References

Chan, K.K.H. and Gibaldi, M., Assessment of drug absorption after oral administration. *J. Pharm. Sci.*, 74 (1985) 388–393.

Chan, K.K.H. and Gibaldi, M., Evaluating drug absorption after oral administration. Some problems and some solutions. *Eur. J. Clin. Pharmacol.*, 26 (1984) 255–259.

Lanao, J.M., Vicente, M.T., Sayalero, M.L. and Domínguez-Gil, A., A computer program (DCN) for numerical convolution and deconvolution of pharmacokinetic functions. *J. Pharmacobio-Dyn.*, 15 (1992) 203–214.

Langenbucher, F. and Möller, H., Correlation of in vitro drug release with in vivo response kinetics: I. Mathematical treatment of time functions. *Pharm. Ind.*, 45 (1983) 623–628.

Rescigno, A. and Segre, G., *Drug Tracer Kinetics*, Blaisdell, London, 1965.

Ronfeld, R.A. and Benet, L.Z., Interpretation of plasma concentration-time curves after oral dosing. *J. Pharm. Sci.*, 66 (1977) 178–180.

Weiner, D.L., NONLIN 84/PC NONLIN: Software for the statistical analysis of non-linear models. *Methods Find. Exp. Clin. Pharmacol.*, 8 (1986) 625–628.

Yamaoka, K., Tanigawara, Y., Nakagawa, T. and Uno, T., A pharmacokinetic analysis program (MULTI) for microcomputer. *J. Pharmacobio-Dyn.*, 4 (1991) 879–885.

Yano, Y., Yamaoka, K., Aoyama, Y. and Tanaka, H., Two-compartment dispersion model for analysis of organ perfusion system of drug by fast inverse Laplace transform (FILT). *J. Pharmacokinet. Biopharm.*, 17 (1989) 179–202.