Modeling in Frequency Domain Used for Assessment of *In Vivo* Dissolution Profile

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Received October 2, 1996; accepted March 26, 1997

Purpose. To present a model-dependent approach for the assessment of the *in vivo* drug dissolution profile based on *in vitro* data for the multiple unit dosage form, as an alternative to the numerical method proposed in the study by Hayashi et al., *Pharm. Res.* **12**:1333–1337 (1995).

Methods. The data for aspirin granules administered to healthy subjects obtained in the above mentioned study were re-evaluated. The subject dissolution system was considered to consist of two subsystems connected in series, i.e. the subsystem describing the gastric-emptying process and the subsystem describing the intestinal dissolution process. The frequency response method was used to model the subject dissolution system.

Results. The model *in vivo* dissolution profile of aspirin, assessed as the integral of the model weighting function of the subject dissolution system, was in agreement with the *in vivo* cumulative absorption profile calculated by the Wagner-Nelson method.

Conclusions. Comparison of dynamic properties of the subject dissolution system with the subsystem describing the gastric-emptying process yielded quantitative confirmation of the decisive role of the gastric-emptying process in the *in vivo* drug dissolution after administration in the multi unit dosage form.

KEY WORDS: aspirin; pharmacokinetics; dissolution; weighting function; convolution; bioequivalence.

INTRODUCTION

Hayashi *et al.* (1) proposed a numerical convolution method for the assessment of drug dissolution profiles in the gastrointestinal (GI) tract based on *in vitro* data for the enteric-coated multiple unit. The goal of our study was to present an alternative model-dependent approach, utilizing the theory of linear dynamic systems and the system modeling in the frequency domain (2).

MATERIALS AND METHODS

Materials

In study (1), enteric-coated aspirin granules were administered to healthy subjects. The enteric-coated $BaSO_4$ granules were administered concurrently to determine the gastric-emptying rate of the subject. The dissolution profile of aspirin in the GI and the absorption profile in the systemic circulation were assessed by the numerical convolution and by the Wagner-Nelson method (3), respectively. In our study, the data from Table II and Table III of study (1) were re-evaluated and the results for the representative subject Y.S. are presented.

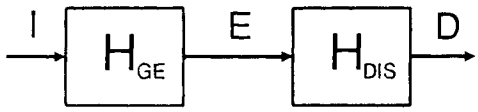

Fig. 1. Schematic representation of the subject dissolution system $H_{DIS,GE}$. H_{GE}—subsystem describing the gastric-emptying process, H_{DIS}—subsystem describing the intestinal dissolution process, D—aspirin dissolution rate in the GI tract, I—input of aspirin granules, E—gastric-emptying rate.

System Definitions

In our study, the subject dissolution system $H_{DIS,GE}$ was considered to be complex and consisting of two subsystems connected in serial, i.e. the subsystem H_{GE} describing the gastric-emptying process and the subsystem H_{DIS} describing the intestinal dissolution process (Figure 1). The system $H_{DIS,GE}$, the subsystems H_{GE} and H_{DIS} were defined using their transfer functions (4) expressed by Eq. 1, Eq. 2, and Eq. 3, respectively

$$H_{DIS,GE}(s) = \frac{D(s)}{I(s)}, \tag{1}$$

$$H_{GE}(s) = \frac{E(s)}{I(s)}, \tag{2}$$

$$H_{DIS}(s) = \frac{D(s)}{E(s)}, \tag{3}$$

in the Laplace s-domain, where D was aspirin dissolution rate in the GI tract, I was the input of aspirin granules, and E was the gastric-emptying rate. Eq. 4 was written for the transfer function $H_{DIS,GE}(s)$ (4)

$$H_{DIS,GE}(s) = H_{DIS}(s)\, H_{GE}(s). \tag{4}$$

Assessment of *In Vivo* Dissolution Profile

Neither the subsystems H_{GE}, H_{DIS} nor the system $H_{DIS,GE}$ were available for measurement and thus the following procedure was used to obtain their model transfer functions:

- The model transfer function $H_{M_{GE}}(s)$ was estimated using the *in vivo* system $H_{GE,REF}$, corresponding to the administration of $BaSO_4$ granules to the subject, and defined by Eq. 5

$$H_{GE,REF}(s) = \frac{E_{BaSO_4\ gran.}(s)}{I_{BaSO_4\ gran.}(s)}, \tag{5}$$

where $E_{BaSO_4\ gran.}$ was the gastric-emptying rate of $BaSO_4$ granules after administration in the form

$$I_{BaSO_4\ gran.}(t) = Dose_{BaSO_4}\delta(t), \tag{6}$$

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0724-8741/97/0700-0860$12.50/0

t was time, and $\delta(t)$ was the Dirac delta pulse. Analogously to study (1), the properties of the subject subsystem describing the gastric-emptying rate were assumed to be similar for both aspirin and $BaSO_4$ granules and thus $H_{M_{GE}}(s)$ was considered to be similar to $H_{M_{GE,REF}}(s)$

$$H_{M_{GE}}(s) \simeq H_{M_{GE,REF}}(s). \quad (7)$$

- The model transfer function $H_{M_{DIS}}(s)$ was estimated using the *in vitro* system $H_{DIS,VITRO}$, defined by Eq. (8)

$$H_{DIS,VITRO}(s) = \frac{D_{aspirin\ gran.}(s)}{I_{aspirin\ gran.}(s)}, \quad (8)$$

where $D_{aspirin\ gran.}$ was the *in vitro* dissolution rate of aspirin granules after the input in the form

$$I_{aspirin\ gran.}(t) = \text{Dose}_{aspirin\ gran.}\delta(t). \quad (9)$$

Since, in study (1) the *in vitro* dissolution profile was presented in an integral form $\int_0^t D_{aspirin\ gran.}(\tau)\, d\tau$, in our study Eq. 10 was employed to determine the model transfer function $H_{DIS,VITRO}(s)$

$$H_{DIS,VITRO}(s) = \frac{s^{-1}D_{aspirin\ gran.}(s)}{s^{-1}I_{aspirin\ gran.}(s)}, \quad (10)$$

where $s^{-1}\, D_{aspirin\ gran.}(s)$ and $s^{-1}\, I_{aspirin\ gran.}(s)$ were the Laplace transforms of the measured *in vitro* dissolution profile and the integral of the input, respectively (4). Analogously to study (1), the *in vitro* and *in vivo* dissolutions of aspirin granules were assumed to be similar and thus $H_{M_{DIS}}(s)$ was considered to be similar to $H_{M_{DIS,VITRO}}(s)$

$$H_{M_{DIS}}(s) \simeq H_{M_{DIS,VITRO}}(s). \quad (11)$$

- The model transfer function $H_{M_{DIS,GE}}(s)$ was estimated as the product of $H_{M_{GE}}(s)$ and $H_{M_{DIS}}(s)$

$$H_{M_{DIS,GE}}(s) = H_{M_{GE}}(s)H_{M_{DIS}}(s). \quad (12)$$

The model transfer functions were used in the form of Eq. 13

$$H_M(s) = G_M \frac{a_0 + a_1 s + a_2 s^2 + \cdots + a_n s^n}{1 + b_1 s + b_2 s^2 + \cdots + b_m s^m}, \quad (13)$$

where G_M was the gain, $a_0, \ldots, a_n, b_1, \ldots, b_m$ were the parameters, and n and m were the orders of the numerator and denominator polynomials, respectively. Optimal models of the transfer functions and optimal frequency bands were selected according to the procedure described in study (6), using the Complex Criterion (CC) (5) and the Akaike Information Criterion (AIC) (10) in the frequency and time domain, respectively. Model weighting functions, $W_M(t)$, were determined in analytical form (8), as the impulse responses (4) of the optimal model transfer functions. The model of the *in vivo* dissolution profile of aspirin was assessed as the numerical integral of the model weighting function of the system $H_{DIS,GE}$.

Comparison of System Dynamic Properties

The model parameter MRT_M of the subsystems H_{GE}, H_{DIS} and the system $H_{DIS,GE}$ were determined according to Eq. 14

$$MRT_M = b_1 - \frac{a_1}{a_0}, \quad (14)$$

using the point estimates of the parameters of the optimal model transfer functions (7), (9). To compare dynamic properties of the dissolution system $H_{DIS,GE}$ and the subsystem describing the gastric-emptying rate H_{GE}, the criterion $C_{dyn.}$ expressed by Eq. 15

$$C_{dyn.} = \frac{2 - \int_0^\infty \left| \frac{W_{M_{DIS,GE}}(t)}{G_{M_{DIS}}} - \frac{W_{M_{GE}}(t)}{G_{M_{GE}}} \right| dt}{2} 100\%, \quad (15)$$

was proposed and applied.

The arguments presented were based on the assumption that aspirin kinetics was linear. All calculations were performed using the program CXT-MAIN (http://www.cpb.uokhsc.edu/pkin/pkin.html) (6–10).

RESULTS

The calculated normalized frequency response (5) of the system $H_{GE,REF}$ and its optimal seventh-order model in the frequency band [0,3] *rad* h^{-1} is shown in Figure 2a. The left part of Table I summarizes the values of the CC and AIC criteria corresponding to this model (the first row) and to some other model candidates. The point estimates of the parameters of the optimal model transfer function $H_{M_{GE,REF}}(s)$, used to approximate the model transfer function $H_{M_{GE}}(s)$, are listed in the first column of Table II. Figure 3a illustrates the gastric-emptying

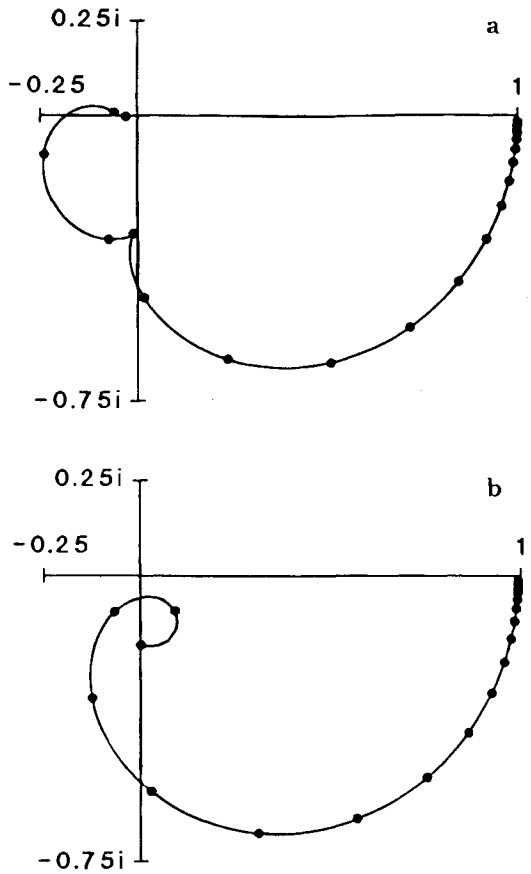

Fig. 2a and 2b. Polar plots of the calculated normalized frequency responses of the systems $H_{GE,REF}$ and $H_{DIS,VITRO}$ (full circles) and their optimal models (full lines) in the complex plane.

Table I. Values of Statistical Criteria of Model Transfer Functions

$H_{M_{GE,REF}}(s)$ $\omega_{max} = 3\ rad\ h^{-1}$			$H_{M_{DIS,VITRO}}(s)$ $\omega_{max} = 10\ rad\ h^{-1}$		
Model	CC	AIC	Model	CC	AIC
5[a]–7[b]	−484.8	−31.7	2–4	−215.2	43.3
4–6	−221.5	−34.9[c]	3–5	−233.7	[d]
3–5	−134.5	[d]	2–5	−225.4	[d]
1–3	−89.8	−33.8	1–4	−52.9	[d]
2–3	−97.6	−33.7	1–3	−35.2	67.8

[a] The degree of the numerator polynomial (n) of the model given by Eq. 13.
[b] The degree of the denominator polynomial (m) of the model given by Eq. 13.
[c] The model produces negative estimates of the gastric emptying rate in the terminal phase of the time interval.
[d] The model has no solution in the time domain.

rate of the subject as determined in study (1) and its approximation by the output of the optimal model $H_{M_{GE}}(s)$, estimated in our study. The model weighting function $W_{M_{GE}}(t)$ is given by Eq. 16 and shown in Figure 4.

$$W_{M_{GE}}(t) = 104.1\ \{3.195\ e^{-0.725t} + e^{-0.690t}[-3.398\cos(0.413t) - 0.42\sin(0.413t)] + e^{-0.545t}[0.196\cos(0.167t) + 0.644\sin(1.067t)] + e^{-0.381t}[6.196\ 10^{-3}\cos(1.747t) - 0.112\sin(1.747t)]\}. \quad (16)$$

The calculated normalized frequency response of the system $H_{DIS,VITRO}$ and its optimal fourth-order model in the frequency band [0,10] $rad\ h^{-1}$ is shown in Figure 2b. The right part of Table I summarizes the values of the CC and AIC criteria

Table II. Point Estimates of Parameters of Model Transfer Functions

	$H_{M_{GE,REF}}(s) \simeq H_{M_{GE}}(s)$	$H_{M_{DIS,VITRO}}(s) \simeq H_{M_{DIS}}(s)$	$H_{M_{DIS,GE}}(s)$
a_0(—)	1.000	0.993	0.993
$a_1(h)$	1.230	0.027	1.249
$a_2(h^2)$	2.105	0.027	2.153
$a_3(h^3)$	0.989	—	1.074
$a_4(h^4)$	0.472	—	0.554
$a_5(h^5)$	0.107	—	0.146
$a_6(h^6)$	—	—	0.015
$a_7(h^7)$	—	—	0.003
$b_1(h)$	4.507	0.630	5.138
$b_2(h^2)$	9.172	0.152	12.167
$b_3(h^3)$	11.175	0.015	17.662
$b_4(h^4)$	9.084	0.001	17.600
$b_5(h^5)$	5.099	—	12.681
$b_6(h^6)$	1.831	—	6.620
$b_7(h^7)$	0.462	—	2.552
$b_8(h^8)$	—	—	0.663
$b_9(h^9)$	—	—	0.100
$b_{10}(h^{10})$	—	—	0.010
$b_{11}(h^{11})$	—	—	0.001

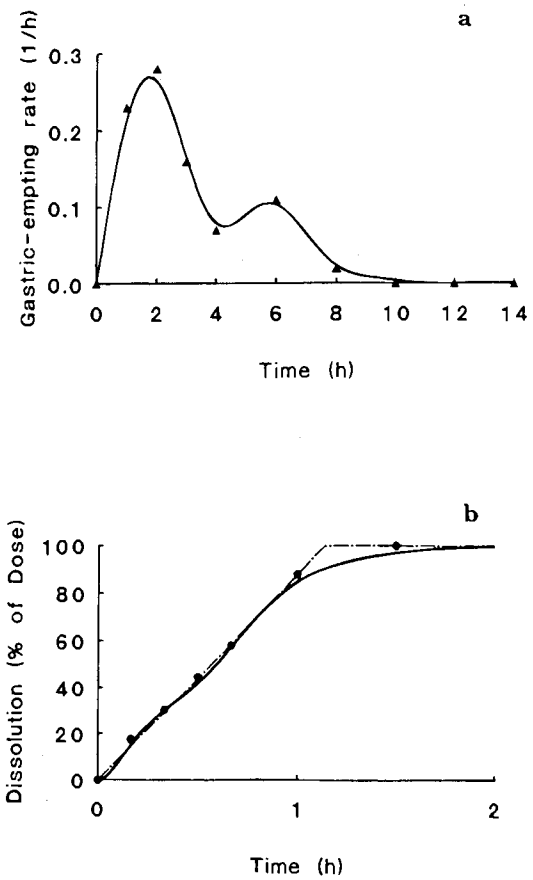

Fig. 3a. Gastric-emptying rate of the subject (triangles) and the output of optimal model $H_{M_{GE}}(s)$ (full line). Fig. 3b. *In vitro* dissolution profile of aspirin granules (full circles), its approximation by the integral of $W_{M_{DIS,VITRO}}(t)$ (full line), and by the integral of $W_{M^0_{DIS,VITRO}}(t)$ (dot-and-dashed line).

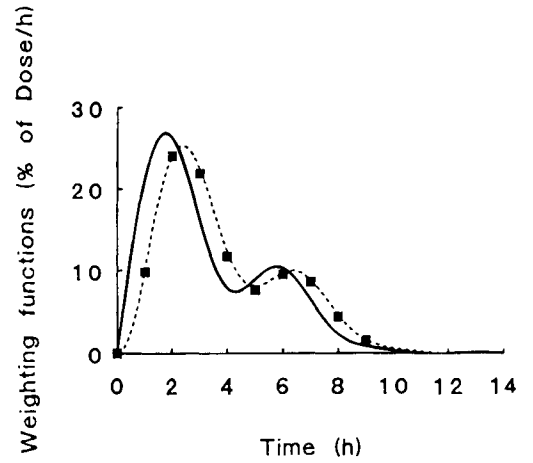

Fig. 4. Model weighting functions $W_{M_{GE}}(t)$ (full line), $W_{M_{DIS,GE}}(t)$ (dotted line), and the model weighting function determined by the numerical convolution of a data set generated by $W_{M_{GE}}(t)$ with a data set generated by $W_{M^0_{DIS,VITRO}}(t)$ (squares).

corresponding to this model (the first row) and to some other model candidates. The point estimates of parameters of the optimal model transfer function $H_{M_{DIS,VITRO}}(s)$, used to approximate the model transfer function $H_{M_{DIS}}(s)$, are listed in the second column of Table II. The corresponding model weighting function $W_{M_{DIS,VITRO}}(t)$ is given by Eq. 17

$$W_{M_{DIS,VITRO}}(t) = 100.2\{e^{-3.060t}[-2.032\cos(1.419t) + 10.837\sin(1.419t)] + e^{-3.211t}[2.032\cos(7.676t) + 0.854\sin(7.676t)]\}. \quad (17)$$

Figure 3b shows the *in vitro* dissolution profile of aspirin granules, as determined in study (1) and its approximation by the integral of $W_{M_{DIS,VITRO}}(t)$.

The point estimates of the parameters of the model transfer function $H_{M_{DIS,GE}}(s)$ of the subject dissolution system, are listed in the third column of Table II. The corresponding model of the dissolution profile of aspirin granules in the subject is shown Figure 5. The same figure illustrates the dissolution profile and the absorption profile of the subject as estimated by the convolution method and Wagner-Nelson method, respectively in study (1). The model weighting function $W_{M_{DIS,GE}}$ is given by Eq. 18 and shown in Figure 4.

$$W_{M_{DIS,GE}}(t) = 104.1\{5.120\,e^{-0.725t} + e^{-0.545t}[-0.365\cos(1.067t) + 0.786\sin(1.067t)] + e^{-0.690t}[-4.825\cos(0.413t) - 2.149\sin(0.413t)] + e^{-0.381t}[0.102\cos(1.747t) - 0.041\sin(1.747t)] + e^{-3.060t}[-0.030\cos(1.419t) + 0.21\sin(1.419t)] + e^{-3.211t}[-2.292\,10^{-3}\cos(7.676t) - 7.25\,10^{-3}\sin(7.676t)]\}. \quad (18)$$

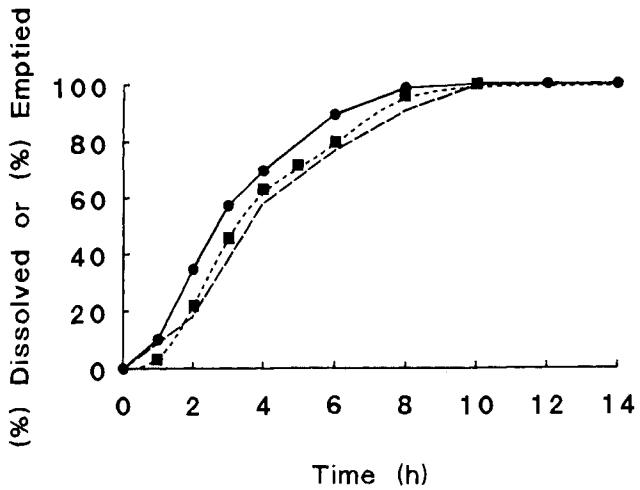

Fig. 5. *In vivo* aspirin dissolution profile (full circles) and aspirin absorption profile (dashed line), as determined in study (1). Model of *in vivo* aspirin dissolution profile, obtained as the integral of $W_{M_{DIS,GE}}(t)$ (dotted line) and the model of the *in vivo* aspirin dissolution profile determined as the integral of the weighting function obtained by the numerical convolution of a data set generated by $W_{M_{GE}}(t)$ with a data set generated by $W_{M^0_{DIS,VITRO}}(t)$ (squares).

The estimation of the model parameter MRT_M of the subsystems H_{GE}, H_{DIS}, and of the system $H_{DIS,GE}$ yielded the values of $MRT_{M_{GE}} = 3.3$ *h*, $MRT_{M_{DIS}} = 0.6$ *h*, and $MRT_{M_{DIS,GE}} = 3.9$ *h*, respectively. It is obvious that

$$MRT_{M_{DIS,GE}} = MRT_{M_{GE}} + MRT_{M_{DIS}}, \quad (19)$$

which is in agreement with Eq. 12 (12). The value of $MRT_{M_{DIS}}$ is approximately 18% of the value of $MRT_{M_{GE}}$, *i.e.* the subsystem H_{DIS} was much faster than the subsystem H_{GE}.

For the given subject, the calculation of the criterion $C_{dyn.}$ yielded the value of 84.3%. The criterion value enabled to quantify that 84.3% of the dynamic properties of the dissolution system were similar to the dynamic properties of the subsystem describing the gastric-emptying process in the subject. This result confirmed that the gastric-emptying process can be considered the decisive process for the *in vivo* drug dissolution after administration in the multi unit type dosage form (1).

DISCUSSION

The points of both frequency responses (Figure 2) can be considered as lying on continuous curves. This is in agreement with our assumption of the possibility to approximate aspirin kinetics by linear models (5).

The high orders of the models of the systems $H_{M_{GE,REF}}$ and $H_{M_{DIS,VITRO}}$ correspond to the loops in the frequency responses (Figure 2) and in the case of the system $H_{M_{GE,REF}}$ to the two peaks in the gastric-emptying rate of the subject (Figure 3a). These findings indicate that the systems are complex and contain time delays (7). From the theoretical point of view, the only optimal model in the form of Eq. 13 of the system with the time delay, is a model with numerator and denominator polynomial degrees converging to infinity (11). Consequently in practice, the higher-order the frequency model, the better approximation of the system with the time delay. For such a model only point estimates of parameters can be reasonably assessed, but not interval ones, and the optimal model must simultaneously fulfill the following conditions: *i*) the optimal maximum frequency ω_{max} is selected in this way that the calculation of the CC criterion yields the minimum value in the frequency domain; *ii*) the optimal frequency model can be reversely transformed into the model output in the time domain, where it produces neither artificial oscillations nor negative estimates; *iii*) the calculation of the AIC criterion yields the minimum value in the time domain (5), (7).

Theoretically, the drug dissolution taking place in an infinite volume under constant conditions obeys zero-order kinetics. The zero-order model weighting function $W_{M^0_{DIS,VITRO}}(t)$ of aspirin dissolution, obtained using the linear regression within the initial 1 *h*, is given by Eq. 20

$$W_{M^0_{DIS,VITRO}}(t) = \begin{cases} 87.9 & \text{for } t \in (0, 1.14]\ h \\ 0 & \text{for } t \in (-\infty, 0]\ h \text{ or } t \in (1.14, \infty)\ h' \end{cases} \quad (20)$$

and its integral is shown in Figure 3b. To approach the finite volume condition, the Weibull function is frequently used in practice. Since the general form of the Laplace transform of that function does not exist, the model $H_{M_{DIS,VITRO}}(s)$ was used in our procedure. The numerical convolution of a data set

generated by $W_{M^0_{DIS,VITRO}}(t)$ with a data set generated by $W_{M_{GE}}(t)$ yields the model weighting function profile nearly identical with $W_{M_{DIS,GE}}(t)$, in spite of the different methods used for their determination and the different orders of $W_{M^0_{DIS,VITRO}}(t)$ and $W_{M_{DIS,VITRO}}(t)$ (Figure 4). Similarly, the integral of the weighting function obtained by the numerical convolution of a data set generated by $W_{M^0_{DIS,VITRO}}(t)$ with a data set generated by $W_{M_{GE}}(t)$ yields the *in vivo* dissolution profile nearly identical with that obtained as the integral of $W_{M_{DIS,GE}}(t)$ (Figure 5).

In study (13), the bioequivalence index was proposed for evaluating the similarity of two plasma concentration curves. The criterion $C_{dyn.}$ is a version of the bioequivalence index, modified for evaluating the similarity of two normalized model weighting functions (5) of two pharmacokinetic systems. It has two limit values, *i.e.* 100% and 0%. The closer the value of the criterion to 100%, the higher the probability that the dynamic properties of the two systems compared would be similar. The closer the value of the criterion to 0%, the higher the probability that the dynamic properties of the two systems compared fail to be similar. The criterion could be used to advantage in bioequivalence studies for overcoming the problem of quantitative comparisons of two rates of extravascular bioavailability (14) of the drug after administration in two dosage forms.

The new procedure presented in our work is model-dependent and methodologically uniform, using exclusively concepts of the theory of linear dynamic systems. In study (1), the same time interval in which the *in vitro* dissolution of aspirin granules was nearly completely was used as the first time interval of the determination of the gastric-emptying rate. Consequently, as can be readily demonstrated, the *in vivo* dissolution profile of aspirin assessed by the numerical convolution method in that study was very close to the integral of the gastric-emptying rate calculated by the rectangular rule, and it practically did not reflect the dissolution rate of aspirin. Our procedure enabled to estimate the *in vivo* dissolution profile of aspirin, reflecting both the dissolution rate of aspirin and the gastric-emptying rate. Moreover, our procedure provided quantitative confirmation of the decisive role of the gastric-emptying process in the *in vivo* drug dissolution after administration in the multi unit dosage form (1).

ACKNOWLEDGMENTS

This work was supported in part by Grant 1021/96 from the Slovak Grant Agency. The authors are grateful to the Journal reviewers for constructive comments on the manuscript.

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