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System-approach methods for modeling and testing similarity of in vitro dissolutions of drug dosage formulations

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Abstract

System-approach based modeling methods are used to model dynamic systems describing in vitro dissolutions of drug dosage formulations. Employing the models of these systems, model-dependent criteria are proposed for testing similarity between in vitro dissolutions of different drug dosage formulations. The criteria proposed are exemplified and compared with the criterion called the similarity factor f_2, commonly used in the field of biomedicine. Advantages of the criteria proposed over this factor are presented.

Keywords: Dissolution; Similarity factor; System approach

1. Introduction

The integrated facility CXT (Complex Tools for Linear Dynamic System Analysis) was introduced in our studies [1,2]. This facility allows to model various dynamic systems, including biomedical systems, in a methodically, conceptually, and computationally uniform way, as shown in our works, e.g. [3–7,9,10]. The goals of this communication are twofold: (1) to present a further example of utilization of the facility CXT, i.e. its use in modeling dynamic systems describing in vitro dissolutions of drug dosage formulations; (2) to propose criteria for testing similarity of in vitro dissolutions of different drug dosage formulations, based on the given models.

2. Theory

To describe in vitro dissolution of the drug dosage formulation, the dynamic system H (thereafter the system H) can be defined in the following way: The product $D(t)$ given by Eq. (1)

$$D(t) = A_{\text{tot}}\delta(t), \tag{1}$$

where A_{tot} is the drug amount in the formulation, $\delta(t)$ is the Dirac delta function, and t is time, can be considered the input of the system H. The drug

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dissolution–time profile $A_{dis}(t)$ obtained by measurements under standard conditions [11,12], can be considered the output of the system H. If a dynamic system satisfies the linearity axioms, it can be mathematically represented by the function called the system transfer function [1,2,13]. For the system H this functions is given by Eq. (2)

$$H(s) = \frac{A_{dis}(s)}{D(s)}, \tag{2}$$

where s is the Laplace variable, and $A_{dis}(s)$ and $D(s)$ are the Laplace transforms of the $A_{dis}(t)$ and $D(t)$, respectively. Since $\delta(s) = 1$, Eq. (2) can be rewritten in the form of Eq. (3)

$$H(s) = \frac{A_{dis}(s)}{A_{tot}}. \tag{3}$$

Static properties of a dynamic system are represented by the parameter called the system gain. Since the system H is an integrating system, i.e. the system integrating its output over time [13], the gain G of this system is given by Eq. (4)

$$G = \lim_{s \to 0} sH(s), \tag{4}$$

in the Laplace domain, or by Eq. (5)

$$G = \frac{\lim_{t \to \infty} A_{dis}(t)}{A_{tot}}, \qquad G \leq 1, \tag{5}$$

in the time domain.

Both static and dynamic properties of a dynamic system are represented by the function called the system weighting function $WF(t)$. The weighting function of the system H can be determined according to Eq. (6)

$$WF(t) = \mathscr{L}^{-1} H(s), \tag{6}$$

where the symbol $\mathscr{L}^{-1}$ stands for the inverse Laplace transformation, or according to Eq. (7)

$$WF(t) = \frac{A_{dis}(t)}{A_{tot}}. \tag{7}$$

Dividing the weighting function $WF(t)$ of a dynamic system by the gain of this system yields the normalized weighting $\overline{WF}(t)$ function of the system. This function represents exclusively the dynamic properties of the system. The physical or biological purport of the gain and weighting function of a dynamic system depends on the system [1,2,4,5,7,9,10]. As follows from Eq. (5), the gain of the system H is the fraction of the total drug amount in the formulation dissolved at time approaching infinity. The time-derivative of the weighting function $WF(t)$ of the system H, given by Eq. (8)

$$R(t) = \frac{dWF(t)}{\mathrm{d}t}, \tag{8}$$

represents the dissolution-rate–time profile $R(t)$ of the drug dosage formulation. Analogously, the time derivative of the normalized weighting function $\overline{WF}(t)$ of the system H represents the normalized dissolution-rate–time profile $\overline{R}(t)$ of the drug dosage formulation. All the systems describing in vitro dissolutions of drug dosage formulations are integrating systems. The time-derivation of the weighting functions $WF(t)$ and/or $\overline{WF}(t)$ of these systems allows to eliminate the common integrating feature of these systems. The profiles $\overline{R}(t)$ represent exclusively the remaining dynamic properties of these systems.

Using the gains G and the normalized profiles $\overline{R}(t)$ of two dynamic systems describing in vitro dissolutions of two drug dosage formulations, the following criteria can be proposed:

- the criterion GC given by

$$GC = \frac{G_1}{G_2} 100\%, \quad \text{for } G_1 \leq G_2, \tag{9}$$

  for testing similarity of the static properties of these systems,
- the criterion RC given by Eq. (10)

$$RC = \frac{2 - \int_0^{\infty} |\bar{R}_1(t) - \bar{R}_2(t)| \, \mathrm{d}t}{2} 100\%, \tag{10}$$

  for testing similarity of dynamic properties of these systems.

Besides the system weighting function, dynamic properties of a dynamic system can be approximately characterized by a single parameter representing the mean time MT of the process described by this system [3,5]. The mean time of the process described by the integrating system H can be determined according to the formula given by Eq. (11)

$$MT = \frac{-\lim_{s\to 0}(\mathrm{d}sH(s)/\mathrm{d}s)}{\lim_{s\to 0} sH(s)}. \quad (11)$$

Analogously to the system gain and weighting function, the physical or biological purport of the parameter MT depends on the process described by a system [1,2,4,5,7,9,10]. The mean time of the process described by the system H is the mean dissolution time of the drug dose formulation [14]. Based on the mean dissolution times MT two drug dosage formulations, the criterion MT given by by Eq. (12)

$$MTC = \frac{MT_1}{MT_2}100\%, \quad \text{for } MT_1 \le MT_2 \quad (12)$$

can be used for approximate testing similarity of the dynamic properties of the systems describing in vitro dissolutions of these formulations [17].

In the criteria given by Eq. (9), Eq. (10), and Eq. (12), the indexes 1 and 2 refer to the system describing the first and second drug dosage formulation, respectively. Each criterion has two limit values, i.e. 100 and 0%. The closer the values of the criteria to 100%, the higher the probability that in vitro dissolutions of two drug formulations compared are similar. The closer the value of these criteria to 0%, the higher the probability that in vitro dissolutions of these formulations fail to be similar. The general form of the criterion RC given by Eq. (10) was proposed in our study [6]. The term $\int_0^\infty |\overline{R}_1(t) - \overline{R}_2(t)|\ \mathrm{d}t$ in this criterion integrates the absolute value of the difference between two normalized profiles $\overline{R}(t)$. Since the area under a normalized profile $\overline{R}(t)$ from time zero to infinity equals 1, in the case of identical profiles $\overline{R}(t)$ the value of this term equals 0.

3. Material and methods

For working examples, in vitro dissolution data of one reference batch and four test batches of the drug were taken from Table 2 published in study [15]. The dynamic systems H corresponding to the individual batches were defined by the transfer functions in the form of Eq. (2). The facility CXT [1], [2] and the model transfer function $H_M(s)$ given by Eq. (13)

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

with the substitution $s = i\omega$, were employed to modal the system H in the frequency domain. G_M is the model gain under the condition $a_0 \simeq 1$. The term $1/s$ represents the integrating property of the systems H. $a_0, \ldots, a_n$, $b_1, \ldots, b_m$ are the model parameters, m represents the model order, i is the imaginary unit, and ω is the radial frequency [13,16]. The numerical forms of the time-domain outputs of the models of the system H were determined as the model responses to the inputs given, employing the Euler method. The analytical forms of the model weighting functions of the systems H were determined using the method described in study [2]. The model-based estimates of the mean dissolution times of the all batches were determined according to the general formula of the mean time of a process described by a dynamic system [3,5], given by Eq. (14)

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

using the estimates of the parameters a_0, a_1 and b_1 of the optimal models in the form of Eq. (13) of the systems H.

At present, the facility CXT forms part of the software package CTDB (Clinical Trial Data Base), a version of which is available from http://nic.savba.sk/sav/inst/exfa/advanced.htm. Another facility of this package, named SIMILARITY TEST, utilizing the criteria given by Eqs. (9), (10) and (12), was employed to test similarity of the static and dynamic properties between the system describing in vitro dissolution of the reference batch and the systems describing in vitro dissolutions of the individual test batches.

4. Results

Table 1 shows the best, estimates with standard errors of the parameters of the optimal models in the form of Eq. (13) of the systems H describing in vitro dissolutions of all the batches. As seen, second-order models were selected for the reference batch and test batches 1, 2, and 3 ($m = 2$), while a first-order model for test batch 4 ($m = 1$).

Table 1
Best parameter estimates with standard errors of the optimal models of the systems describing in vitro dissolutions of the reference and the four test batches

	G_M (–)	a_0 (–)	b_1 (min)	b_2 (min^2)
Reference batch	0.92 ± 0.01[a]	1.00 ± 0.01	23.65 ± 0.29	65.68 ± 4.94
Test batch 1	0.99 ± 0.07	1.03 ± 0.07	35.76 ± 5.31	194.17 ± 64.37
Test batch 2	0.95 ± 0.02	1.00 ± 0.02	23.98 ± 0.61	116.53 ± 8.88
Test batch 3	0.95 ± 0.01	1.00 ± 0.01	20.14 ± 0.96	85.61 ± 14.33
Test batch 4	0.94 ± 0.01	1.00 ± 0.01	8.83 ± 0.79	–

The dissolution data are taken form Table 2, published in study [15].
[a] $\pm$ S.D.

The time-domain outputs of these models and the in vitro dissolution–time profiles measured of all the batches are shown in Fig. 1.

The estimation of the mean dissolution times of the reference batch, test batches 1, 2, 3, and 4 yielded the values: $MT_{\mathrm{M}_{\mathrm{ref}}} = 23.65 \pm 0.29$ min, $MT_{\mathrm{M}_{B1}} = 35.76 \pm 5.31$ min, $MT_{\mathrm{M}_{B2}} = 23.98 \pm 0.61$ min, $MT_{\mathrm{M}_{B3}} = 20.14 \pm 0.97$ min, and $MT_{\mathrm{M}_{B4}} = 8.83 \pm 0.79$ min, respectively. The models of the normalized profiles $\overline{R_{\mathrm{M}}}(t)$ of the systems describing in vitro dissolutions of the reference batch, test batches 1, 2, 3, and 4 are given by Eqs. (15)–(19), respectively

$$\overline{R_{\mathrm{M}_{\mathrm{ref}}}}(t) = 0.0581(\mathrm{e}^{-0.0489t} - \mathrm{e}^{-0.3121t}), \quad (15)$$

$$\overline{R_{\mathrm{M}_{B_1}}}(t) = 0.0449(\mathrm{e}^{-0.0344t} - \mathrm{e}^{-0.1498t}), \quad (16)$$

$$\overline{R_{\mathrm{M}_{B2}}}(t) = 0.0956(\mathrm{e}^{-0.0581t} - \mathrm{e}^{-0.1477t}), \quad (17)$$

$$\overline{R_{\mathrm{M}_{B3}}}(t) = 0.1258(\mathrm{e}^{-0.0712t} - \mathrm{e}^{-0.1641t}), \quad (18)$$

$$\overline{R_{\mathrm{M}_{B4}}}(t) = 0.1131\mathrm{e}^{-0.1131t}, \quad (19)$$

and shown in Fig. 2.

The first two rows of Table 2 lists the values of the criteria *GC* and *RC* obtained in testing similarity of the dynamic system describing in vitro dissolution between the reference batch and the dynamic systems describing in vitro dissolutions of the individual test batches. Since no specific limit values are widely accepted to decide whether two dissolution processes are similar or not [17], to interpret the results given in Table 2, an empirical limit value of similarity higher than 90% [15] is used in this study. As seen in Table 2, the criterion *GC* yielded values higher than 90% for comparison of the reference batch with all the test batches. It follows then that the static properties of the systems describing in vitro dissolutions of all the test batches can be considered similar to those of the reference batch. In other words, the maximum fractions of the total drug amounts

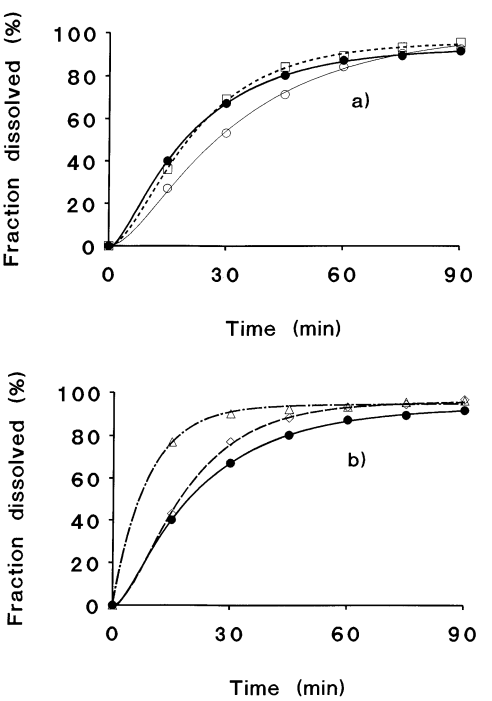

Fig. 1. Dissolution–time profiles measured (taken from Table 2 published in study [15]): the reference batch (points), test batch 1 (circles), test batch 2 (squares), test batch 3 (diamonds), and test batch 4 (triangles). The time-domain outputs of the models of the systems describing in vitro dissolutions of: the reference batch (thick line), test batch 1 (thin line), test batch 2 (dotted line), test batch 3 (dashed line), and test batch 4 (dot-and-dashed line).

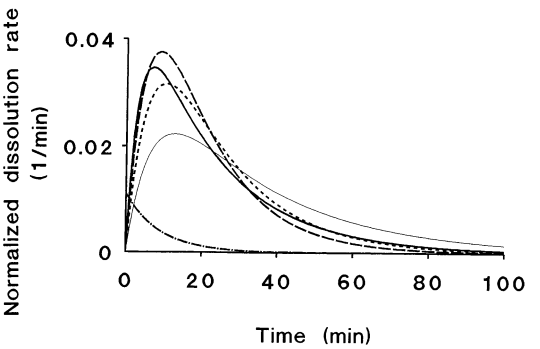

Fig. 2. Models of the normalized dissolution-rate–time profiles of: the reference batch (thick line), test batch 1 (thin line), test batch 2 (dotted line), test batch 3 (dashed line), and test batch 4 (dot-and-dashed line).

dissolved of all the test batches can be considered similar to that of the reference batch, what is in agreement with the results shown in Fig. 1. The criterion *RC* yielded values higher than 90% for comparison of the reference batch with test batches 2 and 3. It follows then that the dynamic properties of test batches 2 and 3 can be considered similar to those of the reference batch. In other words, the normalized dissolution-rate–time profiles of test batches 2 and 3 can be considered similar to that of the reference batch, what is in agreement with the results shown in Fig. 2. The values of the criterion *MTC*, comparing the mean dissolution times of the reference and all the test batches are given in the third row of Table 2. As seen, this approximate criterion for testing similarity of the dynamic properties between the systems describing in vitro dissolutions of the batches compared yielded the results allowing to draw the same conclusions as the exact criterion *RC* only for comparison of the reference batch with test batches 1, 2, and 4.

Finally, it, can be concluded that using the limit value of similarity higher than 90% only the systems describing in vitro dissolutions of test batches 2 and 3 can be considered similar to that of the reference batch, according to both the criteria *GC* and *RC*.

5. Discussion

It is a common way in the field of biomedicine to use various regression functions for various modeling purposes, e.g. polyexponential functions for modeling substance concentration–time profiles, Hill functions for modeling relationships between substance concentrations and effects, or Weibull functions for modeling substance in vitro dissolution–time profiles, etc. In most cases these functions are just models of data, since they take into account only the outcome, e.g. concentration-, or effect-, or in vitro dissolution–time profiles measured, but not the cause, e.g. inputs of substances into the body, or inputs of substances dissolution media. As shown in our previous studies [3–6,8,7,9,10] and in the present communication, using system-approach based modeling methods, various dynamic systems, e.g. systems describing behavior of substances in the body, systems describing relationships between behavior and effects of substances in the body, or systems describing in vitro dissolutions of substances etc. can be modeled using the same model structures. The time-domain counterparts of these model structures are linear ordinary m-order differential equations [13].

Table 2
Similarity between the dynamic system describing in vitro dissolution of the reference batch and the systems describing in vitro dissolutions of the four test batches

	Batch 1	Batch 2	Batch 3	Batch 4
The criterion *GC* (%)	92.4	97.0	96.9	97.9
The criterion *RC* (%)	81.4	93.5	92.6	60.8
The criterion *MTC* (%)	66.1	98.6	85.2	37.3
Value of the f_2 factor	52	71	57	36

Determined using the criteria given by Eq. (9), Eq. (10), and Eq. (12). (The dissolution data and the values of the similarity factor f_2 are taken form Table 2 and Table 3, respectively, published in study [15].)

The common method for testing similarity of in vitro dissolutions of two drug dosage formulations is based on the similarity factor, f_2 given by Eq. (20)

$$f_2 = 50 \log \frac{100}{\sqrt{1 + \sum_{j=1}^{P} (A_{\mathrm{dis}_1} - A_{\mathrm{dis}_2})^2 / P}}, \qquad (20)$$

where P is the number of the time-points of the dissolution measurements, A_{dis_1} and A_{dis_2}, are the dissolution measurements corresponding to the first and second drug dosage formulation, respectively [11,12,15,17,18]. This very simple method has however, the following drawbacks: (1) by increasing the number of sampling points in the time interval in which in vitro dissolutions are almost completed the similarity factor f_2 can be artificially increased, naturally biassing the similarity assessment, as shown in studies [15,17]; (2) the method requires equal sampling time-points for measurements of dissolution–time profiles of the drug dosage formulations and equal drug content in these formulations.

The values of the similarity factor f_2, taken from Table 3 published in paper [15], are given in the last row of Table 2 of our study. Since on comparing the reference batch with test batches 1, 2, and 3 the resulting f_2 values are higher than 50, according to the common interpretation of the similarity factor f_2 [11,12,15,17,18], in vitro dissolutions of these test batches could be claimed similar to that of the reference batch. However, this is is not in agreement with the results shown in Fig. 2 and given in Table 2. As seen, the similarity factor f_2 failed to indicate rather great difference between the dynamic properties of the systems describing the reference and test batch 1.

6. Conclusions

The modeling method used in this study, requires sophisticated modeling work and a new way of thinking of biomedically trained users. The advantage of this method over modeling methods commonly used in the field of biomedicine is the fact that it allows to model various biomedical dynamic systems in a methodically, conceptually, and computationally uniform way. The model-dependent criteria *GC* and *RC* proposed in this study for testing similarity of in vitro dissolutions between different drug dosage formulations have the following advantages over the similarity factor f_2: (1) they require neither equal sampling time-points for measurements of in vitro dissolution–time profiles of drug dosage formulations, nor equal drug content in these formulations; (2) they are not influenced by increasing the number of sampling points in the time interval in which in vitro dissolutions are almost completed; (3) they are more sensitive to differences between in vitro dissolutions of drug dosage formulations than the similarity factor f_2; (4) they allow to test exactly similarity of dynamic properties of the systems describing in vitro dissolutions of drug dosage formulations; (5) they express similarity of in vitro dissolutions between drug dosage formulations in percentages, i.e. in a more straightforward way than does the similarity factor f_2; (5) they allow to differentiate between similarity of static and dynamic properties of systems describing in vitro dissolutions drug dosage formulations.

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