Arh. farm. 2024; 74: 105 – 117 *Review article/Pregledni rad*

Quantitative evaluation of dissolution profiles - from simple approaches to advanced chemometrics

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Received: 11 March 2024; Revised in revised forme: 17 April 2024; Accepted: 20 April 2024

Abstract

Many forms of drugs are designed to undergo dissolution upon oral administration. The kinetics and efficiency of this process are critical parameters to be controlled. The methods of its evaluation are described in official guidelines issued by the Food and Drug Administration (FDA), European Medicines Agency (EMA) and World Health Organization (WHO). Many approaches of comparison have been proposed, because these guidelines are not limited to a particular mathematical method. This review summarizes the current state of this topic, covering both model-dependent and model-independent methods, as well as multivariate ideas. The references have been chosen to be the most important papers in the field, so that they can be treated by the reader as the best possible recommendations for further reading.

Key words: dissolution profiles, model-dependent, model-independent, chemometrics

https://doi.org/10.5937/arhfarm74-49757

Introduction

Drugs are a special class of products because the consumer is not able to assess their quality. Therefore, their control system is very sophisticated and release to the market is dependent on passing rigorous quantitative and qualitative tests.

Oral drug forms are designed to undergo dissolution upon administration. The kinetics and efficiency of this process are critical parameters. During the dissolution test, a tablet is placed in an aqueous medium under controlled conditions. Then, small samples of this solution are taken at appropriate time intervals. The quantitative analysis results in a dissolution profile: a curve representing the process as a function of time. In most cases, the vertical axis is scaled to present the percentage of the released drug instead of an absolute quantity.

An ideal dissolution profile has several mathematical properties. First, it starts from zero and finally reaches 100%. In practice, it approaches this value asymptotically, reaching the sufficient level after an appropriate time. An ideal curve is also monotonically increasing: there are no two consecutive points where the released amount of drug decreases. In practice, small deviations to these assumptions may be present due to random errors.

Official guidelines

Dissolution study is often a part of routine drug control. Another application is the procedure of drug bioequivalence testing. In this field it becomes even more critical, because in many cases the drug innovator can request the waiving of an *in vivo* test if the drug is produced in immediate-release solid oral dosage forms (1, 2). In this case, dissolution study is the only tool to prove the bioequivalence of the drug.

The decision about the waiving possibility is done using the Biopharmaceutic Classification System (BCS)(3-5). It divides drugs into four classes:

I. High Solubility – High Permeability
II. Low Solubility – High Permeability
III. High Solubility – Low Permeability
IV. Low Solubility – Low Permeability.

The first guidance, published in 2000 by the Food and Drug Administration (FDA), recommended that the studies could be waived for class 1 substances (1). Similar documents were later published by the World Health Organization (WHO) and the European Medicines Agency (EMA). The last one extends the possibility of waiving to class 3 drugs (6).

The current ICH M9 guidelines (7), adopted by the EMA in 2020 and the FDA in 2021, state that “a drug product is eligible for a BCS-based biowaiver provided that the drug substance(s) satisfy the criteria regarding solubility and permeability (BCS Class I and III), the drug product is an immediate-release oral dosage form with systemic action, and the drug product is the same dosage form and strength as the reference product”. It

excludes buccal and sublingual formulations from eligibility. Dissolution curve is made with a paddle or basket apparatus in 900 ml or less medium with 37±1°C temperature, in three acidities: pH 1.2, pH 4.5, and pH 6.8. BCS Class I drug substances should display either very rapid (≥85% in ≤ 15 minutes) or rapid dissolution (≥85% in ≤ 30 minutes).

Before the new ICH guidelines, there were no special recommendations about the method which should be used to compare dissolution profiles during a bioequivalence study. Any method could be chosen to prove similarity if it was adequately justified. The newest guidelines favor the f2 coefficient (mentioned later) over other methods.

Comparison methods

In general, the methods used for comparison can be divided into three main groups (8):

1. Model-independent univariate methods, where the curves are not fitted to any equation, but the comparison is based on the values of particular time points.
2. Model-independent multivariate methods, where the curves are treated as points in multivariate space and appropriate chemometric methods are applied to determine the similarity between them.
3. Model-dependent methods, where the curves are fitted to an equation by nonlinear regression and the comparison is done between the parameters of the fitted equations.

Model-independent univariate methods

The simplest choice is to use only one time point and to collect a sample group of dissolved percentage values for the tested and the reference formulation (9). The difference between the means is computed with a 90% confidence interval (in a manner analogous to the *t* test with pooled variance). If the observed interval is shorter than the allowed intra-batch variability, the profiles are considered equal. Chow and Ki (10) proposed simpler equivalence limits, based on ratios.

Nevertheless, the most common choice is to compare whole dissolution profiles. Simple methods are based on the ratio between a coefficient of the tested curve to the analogous parameter of the reference one (11, 12). The most popular are the ratios of the area under the dissolution curve (AUC), and the ratios of mean dissolution time (MDT):

$$\mathrm{MDT} = \frac{\sum_{j=1}^{n} t_j \, \Delta \mathrm{M_j}}{\sum_{j=1}^{n} \Delta \mathrm{M_j}}$$

where j is the time point number, n is the number of times, t_j is the time at midpoint between t_j and t_{j-1}, and ΔM is the amount of drug dissolved between these time points. The idea behind this parameter is the same as the one of mean residence time (MRT) in pharmacokinetics, as it is based on statistical moment analysis. For a detailed discussion about MDT and other coefficients based on moments, the reader is referred to the paper by Pinto at al. (13).

One of the oldest coefficients not based on the ratio, proposed by Moore and Flanner in 1990s, is the f_1 index (14):

$$f_1 = 100\left\{\frac{\sum_{k=1}^{p}|\bar{X}_k - \bar{Y}_k|}{\sum_{k=1}^{p}\bar{X}_k}\right\}$$

This is a difference measure, so it equals zero when profiles are identical and increases proportionally with increasing dissimilarity.

This index is not frequently used in practice, as the similarity factor f_2 (15) has become more popular. It can be treated as a logarithmic transformation of the sum of squared differences between the profiles. It behaves in the opposite manner – the value of 100 means that the profiles are exactly the same, and when the difference increases, it decreases proportionally to zero:

$$f_2 = 50\log_{10}\left(100\left[1 + \frac{1}{p}\sum_{k=1}^{p} w_k(\bar{X}_k - \bar{Y}_k)^2\right]^{-\frac{1}{2}}\right)$$

The statistical properties of this index were extensively studied by Ma et al. and its properties (as a random variable) are known, including the probability density function and its first two moments under the assumption of multivariate normality (16), as well as considerations of the covariance structure. There are also earlier simulations by Liu et al. (17). Several statistical tests for the comparison of two profiles using this index were designed by Bartoszyński et al. (18). They are: an extension of the Mann–Whitney test comparing the variance within sets of profiles and between the sets, an extension of the Kolmogorov-Smirnov *D* statistic comparing empirical cumulative distribution functions, as well as and an adaptation of the chi-squared test.

Current ICH guidelines (7) state that two dissolution profiles are considered similar when the value is greater or equal to 50. When both products have 85% or more of the drug dissolved in 15 minutes, a comparison with this coefficient is unnecessary and the dissolution profiles are considered similar. When the coefficient of variation is too high (more than 20% at early time points up to 10 minutes, more than 10% at other time points), the calculation is considered inaccurate and a conclusion on similarity in dissolution cannot be drawn.

Another widely used coefficient is the Rescigno index (19):

$$\xi_i = \left(\frac{\int_0^\infty |c_r(t) - c_x(t)|^i dt}{\int_0^\infty |c_r(t) + c_x(t)|^i dt}\right)^{1/i}$$

where c_r is the reference concentration and c_x the measured concentration, while i is a positive integer. It always lies between 0 and 1, where 0 means identical profiles.

Gohen and Panchal introduced a coefficient called the similarity factor (20):

$$S_d = \frac{\sum_{t=1}^{n=1} |\log \mathrm{AUC}_{rt} - \log \mathrm{AUC}_{tt}|}{n-1}$$

where *n* is the number of data points collected during the dissolution test, and AUC_{rt} and AUC_{tt} are the areas under the curves of the dissolution profiles of reference and test formulation, respectively. It equals zero for identical profiles and increases with the differences between them.

In 1970s, Khan and Rhodes introduced a concept called dissolution efficiency (21, 22):

$$\mathrm{DE} = \frac{\int_{t1}^{t2} y\, dt}{y_{100}\,(t_2 - t_1)} * 100\%$$

where *y* is the percentage of dissolved product and y_{100} is the maximum achievable dissolved percentage. It can be interpreted as the area under the dissolution curve between two chosen time points, expressed as the percentage of maximum possible dissolution at the same time. In most cases, it is preferable to choose a time interval with a corresponding dissolution value ranging from 70% to 90%.

Dissolution profiles can be also compared using the Analysis of Variance (ANOVA) (23), which is also classified as a model-independent approach. The reason for this assignment is that, although ANOVA relies internally on a linear model, the data are not fitted to any equation. The time points of one sample can be considered as repeated measures of the same object, so the repeated design of ANOVA is used. By incorporating time points as the first factor and formulations as the second one, such a test can answer three questions: whether the data are significantly different at each time level (between time points), whether they are significantly different among the drug products, as well as whether there is a significant time x drug interaction, which would mean that the dissolution profiles are not parallel.

It is possible to introduce three factors to the analysis: tablet (sample), batch and time point. In this case, a usual three-way ANOVA cannot be applied. The tablet is a factor which is nested in the batch. Moreover, it is a random effect, whereas the batch and time are fixed ones. With these facts in mind, linear mixed effect models can be applied. Adams et al. (24) published a comprehensive paper with a strong and clear theoretical introduction on how to apply such an approach for dissolution testing and what advantages it has.

Model-dependent methods

Model-dependent methods rely on fitting a curve to the data. Regardless of the used equation, the model can be modified to contain a delay (most often denoted as T_{lag}). All models with an asymptote can be also rewritten to use a variable modelled parameter instead of the fixed 100%. For the sake of simplicity, we omit these modifications, as they

could result in too many combinations to consider. The models described below are summarized in Figure 1, with mathematical connections between them.

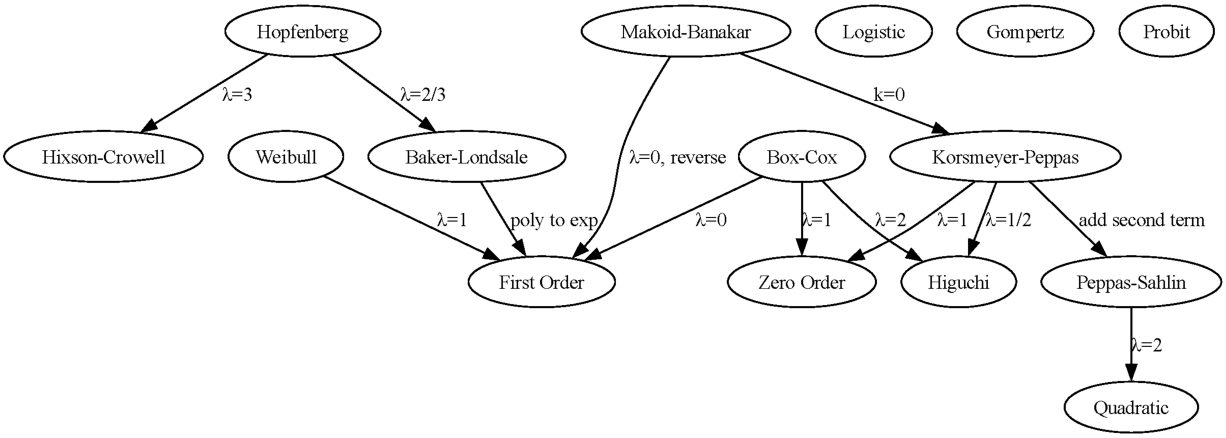

Figure 1. Connections between models (equations) fitted to dissolution profiles. The arrows connect two models, when the first is a special case of the second. The models not connected with any other model cannot be treated as a special case of another one

Slika 1. Veze između modela (jednačina) koje odgovaraju profilima rastvaranja. Strelice povezuju dva modela u slučaju kada je prvi poseban slučaj drugog. Modeli koji nisu povezani ni sa jednim drugim modelom ne mogu se smatrati posebnim slučajem drugog

The simplest model describing a drug release is a linear equation, assuming zero-order kinetics (12, 25, 26):

$$F = k_0 \cdot t$$

where F is the fraction of released drug, t is the time, and k_0 is a kinetic constant. Zero-order kinetics is quite rarely used in practice, because linear dependence occurs only in exceptional situations, for instance in controlled drug release systems. In most cases, the release process meets the first-order kinetics theory, so it can be modelled by a reversed exponential curve (11, 27):

$$F = 1 - e^{-k_1 \cdot t}$$

This equation represents the asymptotically monotonous function, increasing from the origin to the asymptote located at the value equal to one. The k_1 constant is the only parameter to be modelled, hence the interpretation is quite simple. An additional advantage of this model is that it can be fitted by ordinary least squares regression after logarithmic transformation:

$$\log(1 - F) = -k_1 \cdot t$$

Many researchers have looked for other equations presenting monotonously increasing nonlinear dependences, which resulted in several other proposals presented in the literature. For example, it can be assumed that the fraction of released drug is proportional to the square root of time, like in the Higuchi model (28-30):

$$F = k \cdot t^{0.5}$$

This equation does not represent an asymptotic dependence, but in practice it frequently models the release in the same efficiency as the exponential first-order curve. It can be also modelled by linear regression.

For cases that does not fit to any of above models, the equation with a free exponent was proposed by Korsmeyer and Peppas (12, 30-32):

$$F = k \cdot t^{\lambda}$$

Despite the nonlinear appearance, this equation can also be transformed to a linear form and fitted by linear regression techniques:

$$\log F = \log k + \lambda \log t$$

Another way to extend the modelled dependence and change it to curvilinear is to add the second term with an exponent. Several variants have been proposed, but the first and the most obvious idea is to add the second quadratic term (11, 12):

$$F = k_a t + k_b t^2$$

or to add a term with the square root of the time:

$$F = k_a t^{1/2} + k_b t$$

The last equation is known as the Peppas-Sahlin basic model (33). Combining the ideas, both are special cases of the equation, when the second term has an exponent twice lower than the first one:

$$F = k_a t^{\lambda} + k_b t^{2\lambda}$$

which is referred to as the extended Peppas-Sahlin model. The optimal exponent can be evaluated by searching for the optimal value (fitting each value on the grid with the linear regression). Another method is to treat the whole equation as a nonlinear one, and to fit by a nonlinear regression algorithm.

The dissolution profiles can be also modelled by other equations, with no strict connection with the previous ones (these are not linked with other ones in Figure 1). One idea is to combine a linear (zero-order) increasing term with a decreasing exponential multiplier:

$$F = k_a \cdot t^{\lambda} \cdot e^{-k \cdot t}$$

The resulting equation was proposed by Makoid and Banakar in the 1990s (34). The exponential term in the first-order model can be also extended by multiplication or division and raising to some variable power, becoming the Weibull equation (9, 35-37):

$$F = 1 - e^{-\frac{t^{\beta}}{\alpha}}$$

The Gompertz equation (9, 11, 27, 36) can be also used. The idea is to use a double exponential function, which reverses its behavior and increases instead of decreasing. Two parameters describe the shape of the curve:

$$F = e^{-\beta \cdot e^{-k \cdot t}}$$

Lee et al. proposed using the Box-Cox transformation on the F/(1-F) expression (38):

$$\begin{cases} \dfrac{\left(\dfrac{F}{1-F}\right)^{\lambda} - 1}{\lambda} & \text{for } \lambda \neq 0 \\ \log\left(\dfrac{F}{1-F}\right) & \text{for } \lambda = 0 \end{cases}$$

The incorporation of the Box-Cox transformation allows seamless transition between various exponents and the natural logarithm. In practice, this model can fit to the data in a better way.

There is also the possibility of treating tablets as a random effect (as has been previously mentioned in ANOVA) by using nonlinear mixed effect models. For a comprehensive tutorial, the reader is referred to another paper by Adams et al. (39).

As there are numerous models, and each can also be modelled with a delay or free maximum amount term, the proper selection of used models must often be carried out. It can be done with standard criteria dependent on the adequacy of the fit and model complexity, such as the Akaike's Information Criterion (AIC) or Model Selection Criterion (MSC) (40). When an appropriate optimal model is fitted to the reference and investigated profile, the similarity of the two curves can also be assessed in various ways, such as the Chow test (41), or by inserting a dummy variable in the linear model (indicating the formulation), and then testing the significance of this factor in the linear model. There are also specially designed tests based on the Hotelling T2 statistic (27).

Multivariate methods

Multivariate methods treat dissolution profiles as points in multivariate space of dimensionality equal to the number of time points.

The dimensionality can be reduced to emphasize only the significant trends and differences by unsupervised multivariate analysis methods. Some hidden details of dissolution profiles (impossible to notice visually or by univariate methods) can also be detected, simultaneously with similarity analysis.

Multivariate chemometric methods are often described as something which is not connected with statistical inference at all. This is due to problems with multivariate distributions of random variables. However, many of the methods were elaborated by statisticians theoretically, so regardless of data analysis, the profiles can be compared with an appropriate statistic test. For example, in the case of simplest measure of similarity - the Mahalanobis distance (9), its distribution and confidence interval is known. Therefore, similarity can be compared statistically: Saranadasa (42) proposed a multivariate statistical test based on the multivariate mean theory given by Halperin (43).

Principal Component Analysis is a basic method of dimensionality reduction, decorrelation and data compression. It can be also used with many advantages to compare dissolution profiles (44). Projection of profiles to a reduced space allows to visually inspect the between- and within-batch variability.

PCA also provides the possibility to analyze more complex dependences inside profiles, because the overall variability is decomposed to orthogonal (independent) trends. In practice, many things are separated, such as the differences in shape and differences in mean dissolution level, and placed in different components. Irrelevant information is placed in the last component, so it does not interfere with the analysis.

Basic statistical properties of PCA results are also known; however, the literature recommends resampling with replacement or bootstrap to perform any statistical inference about the similarity of profiles. One can also use the newly proposed PCA-CR methodology (45). One of the advantages of the PCA worth mentioning is also the possibility of analyzing data with missing elements (46).

Software

DDSolver, which is an Excel add-in, is a very universal package (40). It can compute a plethora of indices and fit all the mentioned models. The models can be also fitted in any statistical package which is equipped with linear and nonlinear regression, and optionally with mixed-effects models, such as R, Matlab, Statistica or S-plus.

Conclusion

Although the newest ICH M9 guidelines favor the f2 coefficient compared to all other approaches, they are still very valuable addenda during drug development. The authors of this review believe that the cited references will be an invaluable starting point for all readers interested in further researching this topic.

Acknowledgements

N/A

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Łukasz Komsta: Conceptualization; Methodology; Writing - original draft; and Writing - review & editing. **Katarzyna Wicha-Komsta:** Conceptualization; Methodology; Visualization; Writing - review & editing.

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Kvantitativna evaluacija profila rastvaranja - od jednostavnih do naprednih hemometrijskih pristupa

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Kratak sadržaj

Različiti oblici lekova dizajnirani su da se rastvore nakon oralne primene. Kinetika i efikasnost ovog procesa su ključni parametri koje treba kontrolisati. Metode za njihovu evaluaciju su opisane u zvaničnim smernicama koje su izdale Agencija za hranu i lekove (eng. *Food and Drug Administration, FDA*), Evropska agencija za lekove (eng. *European Medicines Agency, EMA*) i Svetska zdravstvena organizacija (eng. *World Health Organization, SZO*). Predloženo je mnogo pristupa za upoređivanje, jer ove smernice nisu ograničene na određenu matematičku metodu. Ovaj rezime predstavlja trenutno stanje u pogledu ove teme, obuhvatajući kako metode zavisne od modela, tako i metode nezavisne od modela, kao i multivarijantne ideje. Reference su odabrane kao najvažniji radovi u oblasti, tako da ih čitaoci mogu smatrati najboljim preporukama za dalje čitanje.

Ključne reči: profili rastvaranja, metode zavisne od modela, metode nezavisne od modela, hemometrija