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# Statistical assessment of dissolution and drug release profile similarity using a model-dependent approach

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**Abstract**

A general multivariate procedure for assessing the similarity of dissolution and drug release profiles was developed. A mathematical model is fit to the data, and Hotelling's $T^2$ test is used to calculate the joint confidence region around the vector of differences between least-squares estimates of the parameters in the model. The method of Lagrange multipliers is used to determine if this confidence region is enclosed within a predetermined similarity region, and profile similarity is claimed if this is the case. The first-order, Gompertz, logistic, second-order, and Weibull models were fit to the *in vitro* extended-release profile of pseudoephedrine HCl from an asymmetric membrane (AM) film-coated osmotic tablet. The first-order model was selected because of its simplicity and because it was the best-fitting model according to a modified form of Akaike's Information Criterion. A nonlinear response surface model was also developed so that the formulator could calculate how much of the AM film coat should be applied in order to obtain the desired drug release profile. The usefulness of this model-dependent procedure was further demonstrated during an analytical method transfer exercise, where it was used to compare the drug release profiles obtained by two independent laboratories; additional research is required, however, before the appropriate acceptance criteria for demonstrating profile similarity can be recommended.


*Keywords:* Dissolution; Mathematical models; Multivariate analysis; Nonlinear regression; Osmotic pumps

## 1. Introduction

Pharmaceutical scientists use *in vitro* dissolution and drug release tests to guide the development of solid oral dosage forms; to monitor the quality, consistency, and stability of those products; to predict *in vivo* drug absorption; and to assess the need for bioequivalence studies after certain scale-up and post-approval changes are made [1,2]. In general, dissolution data are collected at multiple time points so that the resulting profiles can be compared using model-independent (e.g., the $f_2$ similarity factor approach) or model-dependent methods [1–5].

Recently, Likar et al. described the development and validation of a dissolution test for a once-a-day combination tablet containing 10 mg of cetirizine HCl for immediate release and 240 mg of pseudoephedrine HCl for extended release [6]. The dissolution of cetirizine HCl, which is sprayed onto an asymmetric membrane (AM) film-coated tablet of pseudoephedrine HCl, is rapid and independent of solution pH and agitation. The thickness of the non-disintegrating, semipermeable AM coating, on the other hand, controls the rate at which water is imbibed into the core of the osmotic tablet and the rate at which an aqueous solution of pseudoephedrine HCl is pumped out of the tablet through the porous membrane.

This paper focuses on the *in vitro* release of pseudoephedrine HCl from the combination tablet. The objectives of this work were to develop a nonlinear response surface model for the cumulative amount of pseudoephedrine HCl released as a function of time and the weight of the AM film coat, to develop a model-dependent statistical procedure for comparing dissolution and drug release profiles, and to show how this procedure can be used during an analytical method transfer exercise. Unlike the $f_2$ similarity factor approach [7–9], the procedure described in this work takes tablet-to-tablet variability into account. This procedure is also more general than traditional approaches [4,10–13] because it is motivated by a similarity region that properly reflects the idea of similarity and because it can be used with any number of model parameters.

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## 2. Materials and methods

### 2.1. Materials

The quantitative composition of the 240 mg pseudoephedrine HCl tablet cores and AM film coating solution used in this study have been previously published [14]. The tablet cores, which weigh 535 mg each, contain pseudoephedrine HCl, microcrystalline cellulose, hydroxypropyl cellulose, and magnesium stearate. The AM was sprayed onto the tablet cores using a solution of cellulose acetate, polyethylene glycol, acetone, and water. The target weight of the AM film coat was 88.0 mg/tablet after drying. Tablet lots coated with 50–122% of this target weight were obtained by withdrawing samples at different time points during the coating process. The tablets used in the analytical method transfer exercise were coated with 87.4 ± 2.0 mg (95% confidence interval) of the AM film coat; these tablets were also coated with immediate-release cetirizine HCl and taste-masking layers [15].

### 2.2. Dissolution method

The dissolution and HPLC end-analysis methods are fully described in Ref. [6]. The dissolution test employs USP apparatus 2 with paddles rotating at 50 rpm and 1000 mL of deionized water at 37 ± 0.5 °C as the dissolution medium. Six tablets were tested unless otherwise stated. Five-milliliter aliquots of the dissolution medium were withdrawn, and immediately filtered, after 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, and 24 h of testing. These sample solutions were then assayed by a validated reversed-phase HPLC method with UV detection [6], and the cumulative amount of drug released from the tablet was calculated as a percentage of the label claim (i.e., 240 mg/tablet).

### 2.3. Statistical methodology

The nonlinear mathematical models in Table 1 were fit to the dissolution data using MicroMath® Scientist® for Windows™ v.2.01 from MicroMath, Inc. (Saint Louis, MO) or SAS® v.8.02 from SAS Institute Inc. (Cary, NC). These programs use least-squares minimization algorithms that are based on hybrids of the Gauss–Newton method and the method of steepest descent [16,17]. All of the data points were weighted equally. The initial estimates for the model parameters were obtained from a visual examination of the drug release profile, or by using ordinary least-squares regression analysis to fit a linearized form of the model to the appropriately transformed data set. These starting values were then used to obtain the best-fit estimates for each parameter.

To compare two dissolution or drug release profiles, the differences between the parameter estimates from each fit are calculated and a joint confidence region around the vector of mean differences is constructed using Hotelling's $T^2$. The profiles are considered similar if this confidence region falls within a predetermined similarity boundary.

When comparing the dissolution or drug release profiles collected by different laboratories, for example, fits to the individual tablet profiles collected by the Reference Laboratory can be used to determine the similarity boundary. In this case, the similarity boundary is defined in terms of the standard deviations associated with the parameter estimates from the Reference Laboratory. In the one parameter case, assessing similarity is as

Table 1
Mathematical models and best-fit estimates for each parameter[a,b]

| Model | Equation | $R^2$ | MSC | Estimate (S.D.) |
|---|---|---|---|---|
| First-order | $\%R(t) = \%R_{max}\{1 - \exp[-k(t - t_{lag})]\}$ | 0.99953 | 7.20 | $\%R_{max}$ = 98.0 (0.6)% LC<br>$k$ = 0.162 (0.004) $h^{-1}$<br>$t_{lag}$ = 1.22 (0.06) h |
| Gompertz | $\%R(t) = \%R_{max} \exp\{-\alpha_1 \exp[-\beta_1 \log(t)]\}$ | 0.99872 | 6.20 | $\%R_{max}$ = 116 (3)% LC<br>$\alpha_1$ = 4.9 (0.3)<br>$\beta_1$ = 2.4 (0.1) |
| Logistic | $\%R(t) = \%R_{max}\left\{\frac{\exp\left[\alpha_2 + \beta_2 \log(t)\right]}{1 + \exp\left[\alpha_2 + \beta_2 \log(t)\right]}\right\}$ | 0.99949 | 7.13 | $\%R_{max}$ = 102.3 (0.9)% LC<br>$\alpha_2$ = −3.29 (0.07)<br>$\beta_2$ = 4.3 (0.1) |
| Second-order | $\%R(t) = \%R_{max}\left[\frac{t - t_{lag}}{t_{50} + (t - t_{lag})}\right]$ | 0.99727 | 5.44 | $\%R_{max}$ = 123 (3)% LC<br>$t_{50}$ = 5.7 (0.5) h<br>$t_{lag}$ = 1.5 (0.1) h |
| Weibull | $\%R(t) = \%R_{max}\left\{1 - \exp\left[-\left(\frac{t - t_{lag}}{t_d}\right)^{\beta_3}\right]\right\}$ | 0.99958 | 7.17 | $\%R_{max}$ = 97.2 (0.9)% LC<br>$t_d$ = 6.2 (0.2) h<br>$t_{lag}$ = 1.1 (0.1) h<br>$\beta_3$ = 1.05 (0.05) |

[a] $R^2$, coefficient of determination; MSC, model selection criterion; $\%R(t)$, cumulative percent of label claim (%LC) released at time $t$ (h); $\%R_{max}$, asymptotic value of $\%R(t)$ as $t$ approaches infinity; $k$, first-order rate constant; $t_{lag}$, lag time prior to drug release; $\alpha_1$ and $\alpha_2$ are scale parameters; $\beta_1$, $\beta_2$, and $\beta_3$ are shape parameters; $t_{50}$, time required after $t_{lag}$ for 50% of the maximum amount of drug to be released; $t_d$, time required after $t_{lag}$ for 63.2% of the maximum amount of drug to be released.

[b] The equations for the first-order, second-order, and Weibull models are valid for $t \geq t_{lag}$ while the Gompertz and logistic models are valid for $t > 0$. $\%R(t) = 0$ at all other time points $t$.

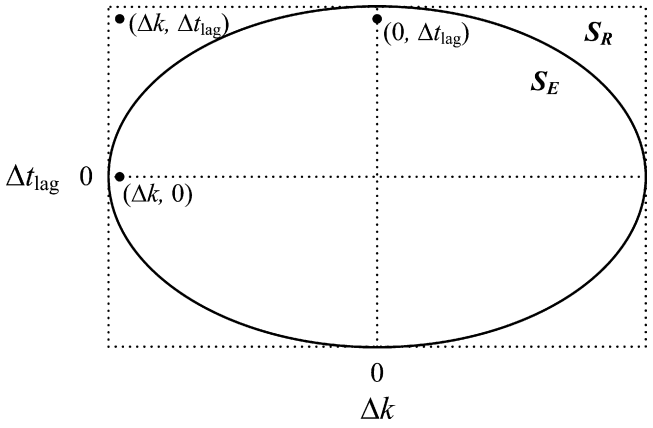


Fig. 1. Comparison of rectangular ($S_R$) and elliptical ($S_E$) similarity regions.

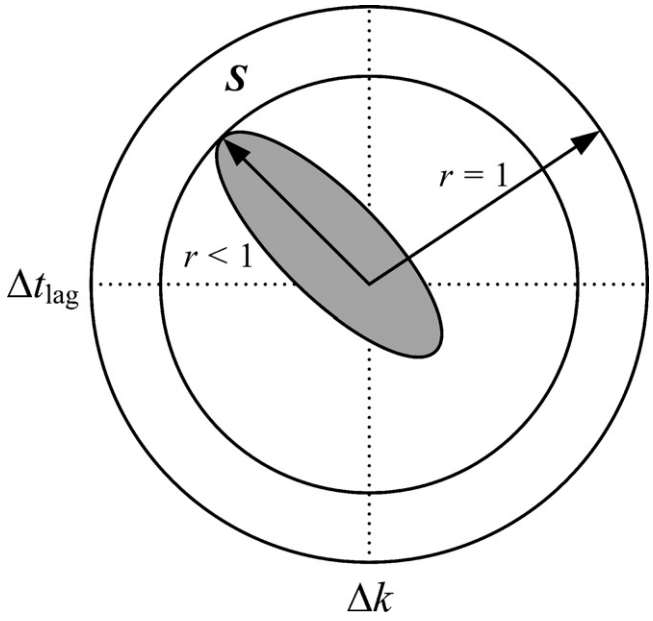


Fig. 2. Hotelling's $T^2$ confidence ellipse (shaded region) for the true differences in the scaled parameters based on the data collected by the Reference and Receiving Laboratories.

simple as looking at the confidence interval around the estimated difference; similarity is claimed if this confidence interval falls entirely within the similarity interval [10]. However, the assessment of similarity becomes more difficult in the multivariate setting. In the case of two parameters, for example, the confidence interval becomes a confidence ellipse. Although many investigators [4,10–13] have used a rectangular similarity region, an elliptical region more properly reflects the idea of "similarity" as a combined measure of several parameters [18]. As shown in Fig. 1, for example, the rectangular similarity region suggests that the combination of parameter differences represented by the point ($\Delta k$, $\Delta t_{lag}$) is "just as similar" as those represented by ($\Delta k$, 0) and (0, $\Delta t_{lag}$); the elliptical similarity region, however, correctly indicates that this is not the case.

In the case of three parameters, the confidence and similarity ellipses become ellipsoids. For example, the first-order model for $\%R(t)$—the cumulative amount of drug released (as a percentage of the label claim) at time $t$—includes three parameters: $\%R_{max}$, the asymptotic value of $\%R(t)$ as $t$ approaches infinity; $k$, the first-order rate constant; and $t_{lag}$, the lag time prior to drug release.

In four- and higher-dimensional cases, a clear and interpretable graphical representation may be difficult or impossible. The mathematical solutions to these problems may appear intractable as well, but the Method of Lagrange Multipliers (MLM) [19] provides an exact solution in any number of dimensions. Furthermore, this method is easily coded and implemented in software such as Mathematica™ v.5.2 from Wolfram Research (Champaign, IL). In the context of showing similarity in the three-parameter case, for example, the MLM finds the origin-centered ellipsoid of maximum radii that intersects the confidence ellipsoid. The profiles are considered similar if this ellipsoid of maximum radii is entirely contained by the similarity ellipsoid.

As discussed in the following section, the problem of comparing two profiles can be further simplified if the parameter estimates are divided by the similarity bounds. In the three-dimensional case, the similarity region then becomes the unit sphere. The dissolution profiles are considered similar if the sphere of maximum radius on the confidence ellipsoid has a radius of less than unity (i.e., the scaled confidence ellipsoid falls entirely within the unit sphere similarity region). To illustrate this concept, the two-dimensional case for $k$ and $t_{lag}$ in the first-order model is shown in Fig. 2; similarity is claimed if the confidence ellipse falls entirely within the similarity region of the unit circle.

### 2.4. Method of Lagrange multipliers

The MLM for similarity testing maximizes a distance function, subject to the constraint that it is tangent to the confidence ellipsoid for the vector of true mean differences in parameters between the test and reference profiles. The MLM is used to find the extrema of the confidence region, which are then compared to the similarity region. To infer similarity, the ellipsoidal confidence region must be contained within the predetermined similarity region.

Without loss of generality, each parameter estimate is scaled by its respective similarity bound (e.g., $2\hat{\sigma}_i$, where $\hat{\sigma}_i$ is the estimated standard deviation for parameter $i$) so that the similarity region is a unit spheroid. If $f(\Delta_1, \Delta_2, \ldots, \Delta_p)$ and $C(\Delta_1, \Delta_2, \ldots, \Delta_p)$ represent the distance function and confidence region, respectively, the goal is to find the maximum of $f$ on $C$ and to compare this extremum to the similarity region. The profiles are considered similar if this extremum is less than the similarity bound. Formally, $f$ and $C$ are defined as follows:

$$f(\Delta_1, \Delta_2, \ldots, \Delta_p) = \sum_{i=1}^{p} \Delta_i^2 \quad (1)$$

and

$$C(\Delta_1, \Delta_2, \ldots, \Delta_p) = \left\{ \boldsymbol{\Delta} : [\hat{\boldsymbol{\Delta}} - \boldsymbol{\Delta}]^{\mathrm{T}} \left[ \left( \frac{1}{n_1} + \frac{1}{n_2} \right) \hat{\boldsymbol{\Sigma}}_p \right]^{-1} [\hat{\boldsymbol{\Delta}} - \boldsymbol{\Delta}] = \frac{(n_1 + n_2 - 2)p}{(n_1 + n_2 - p - 1)} F_{2\alpha, p, n_1+n_2-p-1} \right\} \quad (2)$$

where $\hat{\boldsymbol{\Delta}} = [\hat{\Delta}_1, \hat{\Delta}_2, ..., \hat{\Delta}_p]^{\mathrm{T}} = [\hat{\mu}_{11} - \hat{\mu}_{12}, \hat{\mu}_{21} - \hat{\mu}_{22}, \ldots, \hat{\mu}_{p1} - \hat{\mu}_{p2}]^{\mathrm{T}}$ is the vector of sample mean differences between the laboratory's scaled parameters; $\boldsymbol{\Delta} = [\Delta_1, \Delta_2, \ldots, \Delta_p]^{\mathrm{T}} = [\mu_{11} - \mu_{12}, \mu_{21} - \mu_{22}, \ldots, \mu_{p1} - \mu_{p2}]^{\mathrm{T}}$ is the vector of true mean differences between the laboratory's scaled parameters; $\hat{\boldsymbol{\Sigma}}_p$ is the sample variance-covariance matrix of scaled measurements; $p$ is the number of parameters in the mathematical model used to fit the dissolution data (e.g., $p = 3$ for the first-order model); $n_j$ is the number of tablets tested by laboratory $j$; $\alpha$ is the type I error rate (e.g., 5%) for testing the null hypothesis, $H_0$: $\boldsymbol{\Delta} = \boldsymbol{\Delta_0}$ (e.g., $\boldsymbol{\Delta} = 0$); and $C$ is the $100(1 - 2\alpha)$% confidence ellipsoid for the true differences between the scaled parameters [20]. The mean scaled parameters implicit in Eq. (2) are given by $\hat{\mu}_{ij} = \sum_{k=1}^{n_j} X_{ijk}/m\hat{\sigma}_i n_j$, where $i = 1, 2, \ldots, p$; $j = 1, 2$; $k = 1, 2, \ldots, n_j$; $X_{ijk}$ is the estimate of the $i$th parameter for the $j$th laboratory's $k$th tablet profile; $m$ is a positive real number; and $C$, the set of all $\boldsymbol{\Delta}$ such that the bracketed equality in Eq. (2) holds, defines the surface of the confidence ellipsoid.

If the function $f$ is maximized at $(\Delta_1^0, \Delta_2^0, \ldots, \Delta_p^0)$ on $C$, the MLM claims that the following relationship holds for some scalar $\lambda$:

$$\nabla f(\Delta_1^0, \Delta_2^0, \ldots, \Delta_p^0) = \lambda \nabla C(\Delta_1^0, \Delta_2^0, \ldots, \Delta_p^0) \quad (3)$$

where $\nabla f(\Delta_1^0, \Delta_2^0, ..., \Delta_p^0) = \left[ \frac{\partial f}{\partial \Delta_1^0}, \frac{\partial f}{\partial \Delta_2^0}, \ldots, \frac{\partial f}{\partial \Delta_p^0} \right]^{\mathrm{T}}$, and $\nabla C$ is defined similarly. Such a scalar $\lambda$ is called the *Lagrange multiplier*. The extrema of $f$ are then found by solving the $p + 1$ equations—from Eq. (3) and constraint (Eq. (2))—in $p + 1$ unknowns. Similarity is claimed if the distance function, $f$ (a spheroid), of maximum radius on $C$ is entirely contained in the similarity spheroid $\sum_{i=1}^{p} \Delta_i^2 = 1$ (the unit spheroid).

## 3. Results and discussion

### 3.1. Model selection

The first step in the model-dependent approach is to identify a mathematical function that accurately describes the dissolution profile. As a highly soluble compound, the rate at which pseudoephedrine HCl is released from the osmotic tablet is expected to decrease over time [21–24]. Therefore, the mathematical functions in Table 1 were selected as potential candidates because they explicitly model the rate, shape, and extent of nonlinear growth curves such as dissolution profiles [1–5].

Although some scientists assume that the maximum amount of drug released is equal to 100%, $\%R_{\max}$ is included as a fitting parameter in this work for several reasons. For example, it is unlikely that an individual tablet will contain exactly 100% of the labeled amount of the drug substance. Furthermore, forcing the model to an idealized and artificial asymptotic value may inflate the variances of the other parameter estimates and lead to a similarity region that is artificially larger than it should be; this, in turn, may lead to the false conclusion that the profiles are similar.

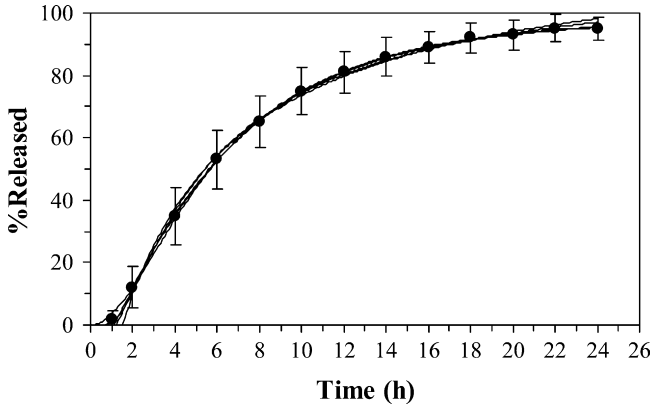


Fig. 3. Cumulative %released profile for pseudoephedrine HCl (mean ± 2S.D.) and fits of the first-order, Gompertz, logistic, second-order, and Weibull models.

As shown in Fig. 3, all of the models seem to fit the data well. The coefficient of determination ($R^2$) for each fit was ≥0.997, and no systematic trends were observed in any of the residual plots. In addition, the standard deviation associated with each parameter estimate was less than 10% of the estimated value.

The Gompertz and second-order models were rejected, however, because the $\%R_{\max}$ estimates for these models were significantly greater than the measured potency of the drug product batch (99.6 ± 1.0% of label claim at the 95% confidence level). In addition, these models had relatively low Model Selection Criterion (MSC) values. The MSC is a modified form of the Akaike Information Criterion (AIC), which is widely used to select the best-fitting model when those under consideration do not contain the same number of parameters [25]. The model with the largest MSC value is considered the most appropriate one [16,26].

While the first-order, logistic, and Weibull models were all acceptable, the first-order model was selected because it is relatively simple (e.g., it only has three parameters and the physical meaning of each parameter is readily apparent) and because it had the highest MSC value.

### 3.2. Formulation development studies

In order to determine how the weight of the AM membrane affects the *in vitro* release of pseudoephedrine HCl from the drug product, tablet cores were coated with 50–122% of the target AM coating weight. The drug release profiles of these lots are shown in Fig. 4, along with the fits ($R^2 \geq 0.998$) of the first-order model. The relationship between each parameter in this model and the percentage of the target AM coating weight ($w$) was obtained by ordinary least-squares regression. As expected for

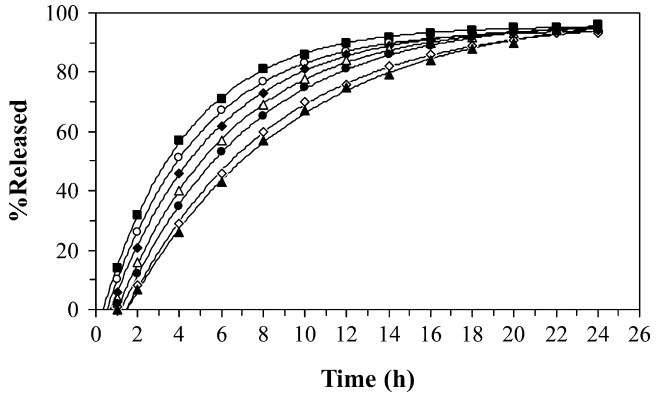


Fig. 4. Mean cumulative %released profiles for pseudoephedrine HCl from tablets coated with approximately 50% (■), 60% (◯), 77% (♦), 86% (Δ), 97% (●), 110% (◊), and 122% (▲) of the target weight of the AM film coat. The solid lines represent the fits of the first-order model to each profile. (adapted from Ref. [6]).

an osmotic tablet (since the weight of the semipermeable membrane is roughly proportional to its effective thickness) [21–23], the lag time increased ($t_{lag} = 0.0174w - 0.53$, $R^2 = 0.973$), and the first-order rate constant decreased ($k = 9.8w^{-1} + 0.059$, $R^2 = 0.952$), as the weight of the semipermeable membrane increased. A slight increase in $\%R_{max}$ with coating weight was also observed ($\%R_{max} = 0.075w + 90.5$, $R^2 = 0.822$).

In order to predict the drug release profile for any tablet lot coated between 50 and 122% of the target weight, the regression equations for $t_{lag}$, $k$, and $\%R_{max}$ as a function of $w$ were used to develop the following nonlinear response surface model:

$$\%R(w,t) = (0.097w + 89.3)\{1 - e^{-(12.5w^{-1}+0.020)[t-(0.0117w-0.17)]}\} \quad (4)$$

This model, which is plotted in Fig. 5, fits the data well in that the $R^2$ value was 0.9997 and the residuals at each time point were less than ±3% of label claim. This equation is also useful.

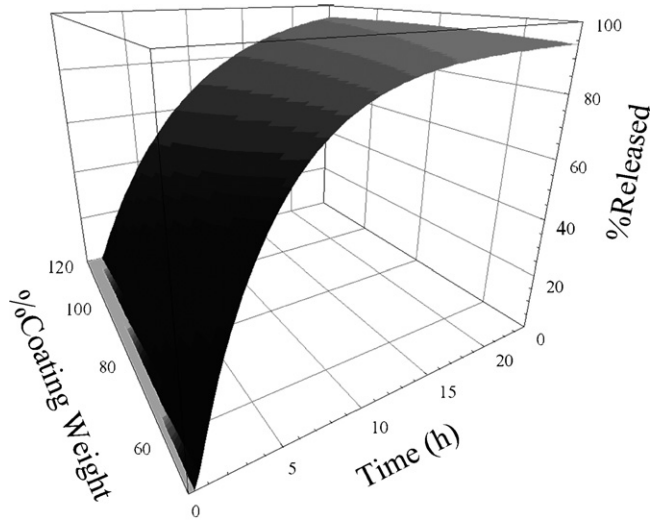


Fig. 5. Response surface for the cumulative amount of pseudoephedrine HCl released as a function of time and AM film-coating weight.

For example, formulators can use this equation to calculate how much of the AM film coat they should apply in order to achieve the desired *in vitro* drug release profile.

### 3.3. Analytical method transfer exercise

Analytical methods are often transferred from one laboratory to another. For example, a method may be developed and validated in one laboratory (the Reference Laboratory), and then transferred to another laboratory (the Receiving Laboratory) where samples are tested during long-term stability studies. The goal of an analytical method transfer exercise is to demonstrate that the Receiving Laboratory can reproduce, within some acceptable tolerance, the results obtained by the Reference Laboratory.

The model-dependent approach developed in this study, along with the hypothetical similarity limits of $\pm 2\hat{\sigma}_i$, was used to compare the drug release profiles obtained by two independent laboratories during an analytical method transfer exercise. Each laboratory tested 12 tablets, and the first-order model was fit to the data for each tablet using the NLIN procedure from SAS® v.8.02. The parameter estimates from each fit are listed in Table 2, while the mean profiles and fits are shown in Fig. 6.

The drug release profiles of the Reference and Receiving Laboratories were considered similar because, as shown in Fig. 7, the 90% joint confidence ellipsoid for the differences in the scaled model parameters was totally enclosed within the similarity region of the unit sphere. That is, the sphere of maximum radius that intersects the confidence ellipsoid has a radius that is less than unity.

It should be noted, however, that the radius of this sphere (0.992) was only slightly less than unity. This observation, along with the visual similarity and $f_2$ value of 91 for the two profiles in Fig. 6, may lead some readers to conclude that the $\pm 2\hat{\sigma}_i$ similarity limits are too conservative. In fact, the choice of $\pm 2\hat{\sigma}_i$ was arbitrary; additional research is required before appropriate acceptance criteria can be recommended. For example, the iterative approach to estimating the similarity bound in the univariate case [27] does not transfer well to the multivariate case because the correlations among the parameters make the necessary calculations analytically intractable.

In addition, Fig. 7 shows that it is the differences in $k$ and $t_{lag}$ that force the extremum of the confidence ellipsoid near the $r = 1$ criterion; the difference in $\%R_{max}$ is not the primary cause. If similarity with respect to $k$ and $t_{lag}$ is considered to be of more importance than with respect to $\%R_{max}$, the similarity region could reflect this if one uses a larger scalar multiple for the standard deviation of $\%R_{max}$. That is, some parameters could be weighted more heavily than others.

### 3.4. Other potential applications of this model-dependent procedure

The statistical procedure developed in this work can be used to compare any pair of dissolution or drug release profiles that can be fit to a mathematical model. For example, this procedure could be used during analytical method development studies to

Table 2
First-order model parameter estimates for individual tablets tested by the Reference and Receiving Laboratories

| Tablet no. | Reference Laboratory | | | Receiving Laboratory | | |
|---|---|---|---|---|---|---|
| | $\%R_{max}$ (%LC) | $k$ ($h^{-1}$) | $t_{lag}$ (h) | $\%R_{max}$ (%LC) | $k$ ($h^{-1}$) | $t_{lag}$ (h) |
| 1 | 98.8 | 0.139 | 1.22 | 100.7 | 0.135 | 1.07 |
| 2 | 98.3 | 0.146 | 1.22 | 96.5 | 0.150 | 1.08 |
| 3 | 97.1 | 0.157 | 1.08 | 99.2 | 0.138 | 1.18 |
| 4 | 97.1 | 0.185 | 0.88 | 99.8 | 0.143 | 1.05 |
| 5 | 100.2 | 0.121 | 1.30 | 96.4 | 0.153 | 1.05 |
| 6 | 99.2 | 0.131 | 1.29 | 99.5 | 0.157 | 1.05 |
| 7 | 95.6 | 0.139 | 1.18 | 96.0 | 0.154 | 1.06 |
| 8 | 102.3 | 0.111 | 1.33 | 100.5 | 0.120 | 1.32 |
| 9 | 100.4 | 0.143 | 1.09 | 100.1 | 0.126 | 1.32 |
| 10 | 97.3 | 0.145 | 1.16 | 97.7 | 0.159 | 1.07 |
| 11 | 101.7 | 0.140 | 1.09 | 99.6 | 0.130 | 1.29 |
| 12 | 95.0 | 0.139 | 1.19 | 98.0 | 0.163 | 0.91 |
| Mean | 98.6 | 0.141 | 1.17 | 98.7 | 0.144 | 1.12 |
| S.D. | 2.3 | 0.018 | 0.12 | 1.7 | 0.014 | 0.13 |

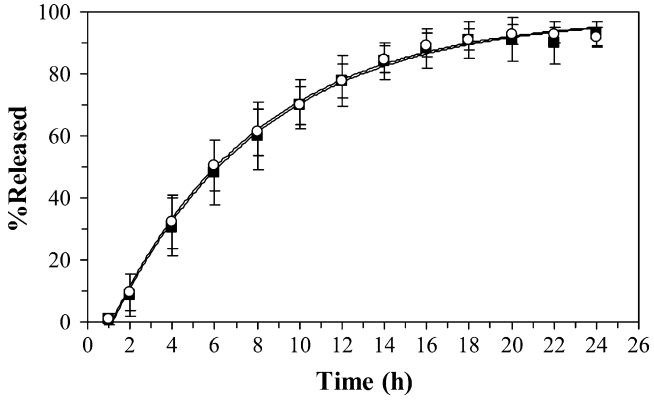


Fig. 6. First-order fits to the cumulative %released profiles for pseudoephedrine HCl (mean ± 2S.D.) collected by the Reference (■) and Receiving (◯) Laboratories.

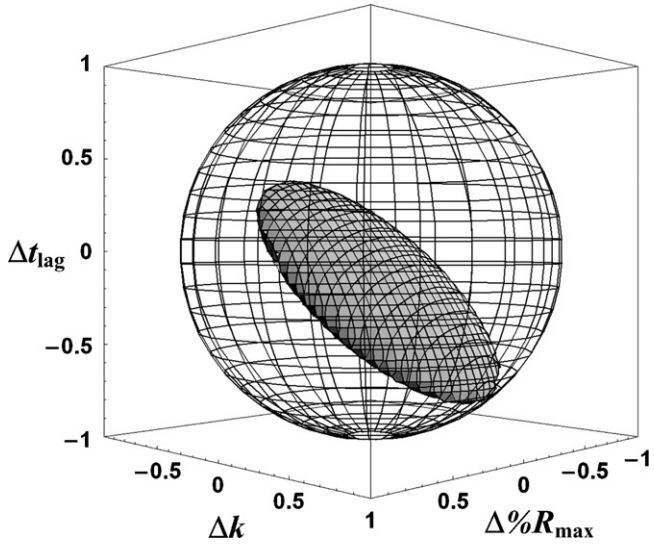


Fig. 7. Unit sphere similarity region and confidence ellipsoid obtained from an analytical method transfer exercise.

compare the profiles obtained using different dissolution media, apparatus, and so forth. Likewise, it could be used during the drug product development process to compare the profiles of different formulations, stability samples, drug product batches, and batches manufactured before and after the scale-up and postapproval changes that are described in various regulatory guidelines (cf. [28,29]). This procedure could also be used to compare the dissolution or drug release profiles of generic and brand name drug products (cf. [30]). It should be noted, however, that additional research is required before the appropriate similarity limits for each of these applications can be recommended.

## 4. Conclusions

A model-dependent multivariate procedure for assessing the similarity of dissolution and drug release profiles was developed and implemented using the method of Lagrange multipliers. This procedure was used to model the *in vitro* extended-release profiles of pseudoephedrine HCl from an osmotic tablet and to compare the drug release profiles collected by two laboratories during an analytical method transfer exercise. This procedure is quite general and could be used to compare any pair of dissolution or drug release profiles.

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