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COMMUNICATION

A Novel Bending Point Criterion for Dissolution Profile Interpretation

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ABSTRACT

A novel bending point criterion was developed and compared with a number of existing criteria for the interpretation of certain dissolution profiles; these comparison criteria were the percentage dissolved at a fixed time point, the fitted Weibull parameters, and the area under the dissolution curve (AUC). The statistical bending point model was applied to dissolution curves that showed linear dissolution. The bending point model is based on a general linear model, and its confidence information is obtained using the variance-covariance matrix of the parameter estimates. Practically, three time points in the linear part and two time points on the plateau level are used for a reliable bending point estimation. A comparative study with three batches and three storage conditions of slow-release mucoadhesive buccal tablets was performed. The relative standard deviation (RSD) values of the bending point were typically between 1% and 5%, which are considerably lower than the corresponding values of the other criteria (typically between 3% and 15%). The bending point criterion is considered robust and stable for the characterization of certain dissolution profiles. Moreover, the bending point has a particular physical interpretation that is helpful in the framework of the slow-release application of this buccal tablet.

Key Words: *Buccal tablet; Dissolution; Model-dependent analysis; Statistics*

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INTRODUCTION

The dissolution test for immediate- and slow-release dosage forms is described in the different pharmacopoeias (1,2). The in vitro dissolution specifications included in the manufacturing and controls section of a Marketing Authorization Application are usually a single- or multiple-point estimate. For instance, for immediate-release drug products that dissolve almost completely within 30 min, compliance with the specification limit is tested using the determination of the average dissolution value of the tested tablets at 15 or 30 min plus or minus 2 to 3 standard deviations (3). A single-point dissolution test does not characterize the dosage form completely; therefore, a dissolution profile and a dissolution profile comparison are recommended in a number of the FDA's Guidances for Industry (4–7). Although this "point estimate" approach is suitable for drug products with rapid dissolution, it may not be adequate for products with either low solubility activities or modified release characteristics (8).

Numerous methods to compare dissolution profiles are proposed in the literature, of which a comparative overview is presented by Polli et al. (9). These methods can be classified into three categories:

1. Approaches based on analysis of variance (ANOVA) (univariate or multivariate).
2. Model-independent approaches (e.g., the ratio of area under the dissolution curves (AUC) or the similarity factor f_2 (4–7,10), which is recommended in the FDA's Guidances for Industry).
3. Model-dependent methods (e.g., first-order model, Weibull model, etc.).

The bending point method presented in this article can be classified as a model-dependent method (category 3). The aim of this paper is to present a novel dissolution curve characterization parameter (dissolution curve bending point) based on multiple time points and reflecting the time at which the dissolution process can theoretically be considered finished. The developed bending point criterion is compared with a number of existing criteria, and its usefulness for slow-release formulations is assessed.

EXPERIMENTAL

Drug Dosage Form Tested

The tablets used were mucoadhesive buccal tablets containing 10.0 mg miconazole nitrate per tablet; they are formulated to obtain a slow release activity of approximately 8 h. Three batches (98L08, 98L09, and 98L10) were packed in aluminum/aluminum blisters and stored for 3 months under three controlled storage conditions (4°C, 25°C, and 50°C).

In Vitro Dissolution Tests

The dissolution experiments were performed with a reciprocating cylinder dissolution apparatus (USP apparatus 3) (2). The dissolution parameters were 21 dips per minute, dissolution medium 250 ml 0.1 N HCl plus 0.5% HPCD (hydroxypropyl-β-cyclodextrin), holding temperature 37°C, 12 ml of sample per vessel. For each dissolution experiment, 6 tablets were used to produce 6 individual dissolution curves. The sampling times were 1, 2, 4, 6, 8, and 9 h. High-performance liquid chromatography (HPLC) measurements were applied to assay the active drug substance released at the different time intervals. The concentration of the drug substance in the dissolution solvent was calculated to express the result in percentage of the labeled content (i.e., 10.0 mg) released.

The collected dissolution data used in this article are presented in Table 1.

Bending Point Statistical Model

The bending point model can be applied when the two following conditions are fulfilled: (1) The dissolution curve is recorded until its plateau level is reached; (2) the dissolution in the first part of the dissolution curve is linear (zero-order kinetics). Although two time points in the linear part and one time point on the dissolution plateau level are sufficient for the implementation of the bending point model, three time points in the linear part and two time points on the plateau level are proposed for a reliable bending point estimation. Although not strictly necessary, the time intervals are preferentially equal.

Before the statistical bending point model may be applied to the dissolution data, it has to be

Table 1

Dissolution (% Released) for Slow-Release Buccal Tablet After 3 Months of Storage at Three Temperatures

		% Released, 4°C, Batch Number			% Released, 25°C, Batch Number			% Released 50°C, Batch Mumber		
Tablet	Time (h)	98L08	98L09	98L10	98L08	98L09	98L10	98L08	98L09	98L10
1	1.0	7.8	7.5	12.2	13.5	13.1	14.6	35.4	45.6	37.6
	2.0	16.7	22.8	24.6	24.9	21.8	29.4	53.1	76.4	62.5
	4.0	42.6	42.9	43.8	50.8	49.0	55.2	97.0	106.0	82.1
	6.0	61.2	60.1	62.2	72.2	71.4	78.6	89.7	101.0	89.2
	8.0	83.5	78.0	79.4	85.4	92.0	89.5	84.2	101.2	91.8
	9.0	80.3	77.6	79.3	85.6	89.6	91.4	89.3	95.6	91.1
2	1.0	8.9	7.2	14.4	17.1	14.4	14.7	38.0	47.2	32.0
	2.0	18.1	14.9	28.0	29.7	26.1	28.4	60.9	73.5	61.6
	4.0	46.2	36.0	51.3	53.1	47.2	48.9	92.8	105.7	89.2
	6.0	68.9	56.2	72.5	80.9	75.9	73.2	92.4	107.7	84.5
	8.0	86.2	72.2	89.3	89.0	87.1	89.8	88.9	116.1	87.3
	9.0	91.7	76.7	92.5	88.5	87.3	87.2	92.1	112.2	83.4
3	1.0	7.8	12.7	12.2	13.5	15.3	13.5	42.0	45.5	37.9
	2.0	15.1	25.9	24.3	26.1	28.5	25.9	76.0	73.4	66.1
	4.0	43.8	47.0	44.3	53.8	50.8	47.2	101.9	110.4	98.4
	6.0	72.4	69.9	65.4	74.9	75.0	72.5	95.4	101.1	86.9
	8.0	90.6	78.3	85.7	86.9	87.0	85.4	96.3	105.8	88.8
	9.0	92.8	77.8	85.8	82.2	85.0	85.7	93.6	107.0	84.6
4	1.0	8.9	6.1	12.8	13.9	15.2	15.0	—	46.4	33.0
	2.0	19.8	17.2	22.9	26.7	29.7	27.4	—	81.2	57.6
	4.0	42.3	37.1	44.3	49.6	50.6	49.6	—	100.3	91.2
	6.0	76.4	61.5	63.2	72.9	75.2	69.1	—	103.2	94.2
	8.0	89.4	80.7	81.7	87.3	88.8	84.7	—	105.8	93.4
	9.0	93.4	83.3	82.2	85.7	86.3	83.9	—	111.3	89.2
5	1.0	8.5	13.5	13.8	16.1	16.8	14.5	43.3	49.3	37.3
	2.0	21.7	24.6	26.8	27.3	29.9	27.0	61.9	80.9	60.1
	4.0	47.7	48.0	48.9	50.5	57.7	48.9	93.5	82.4	89.7
	6.0	69.5	66.7	71.8	73.6	75.2	69.6	95.2	86.0	88.9
	8.0	90.8	82.5	86.4	87.3	86.9	86.9	89.8	84.7	89.5
	9.0	87.8	84.5	86.0	82.4	86.5	85.4	89.5	83.4	91.5
6	1.0	8.1	15.2	12.8	13.8	7.8	13.1	38.6	44.3	33.6
	2.0	14.7	29.3	23.3	25.4	18.4	25.8	64.0	72.2	60.8
	4.0	39.3	50.9	45.7	51.7	44.9	47.3	100.4	100.5	79.9
	6.0	63.1	73.1	68.3	71.4	76.5	71.6	97.6	103.9	92.4
	8.0	85.6	83.6	85.1	86.9	85.7	90.1	95.1	103.5	91.3
	9.0	92.3	83.8	89.3	86.4	85.9	86.5	90.6	100.9	96.4

Analyses were of three batches, 6 tablets per batch.

assessed which time points are considered to be on the dissolution plateau level. It is proposed to use successive linear regression models $Y = \beta_0 + \beta_1 t$ on the last n time points of the dissolution curve (n is successively 2, 3, etc.) until the null hypothesis $H_0 : \beta_1 = 0$ versus $H_1 : \beta_1 > 0$ cannot be retained any more. If, at the first step ($n = 2$) this approach does not yield the assessment of a plateau, the last time point is considered to be on the plateau level. However, such a situation possibly points to a recorded dissolution profile in which the plateau level was not reached yet. Consequently, the bending point model should then be considered less reliable. The linearity in the first part of the dissolution

curve is statistically assessed by fitting a second-order model $Y=\beta_0+\beta_1 t+\beta_2 t^2$ to the experimental data in the first part of the dissolution curve, followed by testing the null hypothesis $H_0:\beta_2=0$ versus $H_1:\beta_2\neq 0$. If the null hypothesis is retained, the quadratic term in the regression equation is not significant; hence, the first part of the dissolution curve is considered linear.

For the experimental data presented in Table 1, the number of time points on the plateau dissolution level statistically assessed with the above-described method are the same for all batches within each storage condition. More particularly, two and four time points on the plateau level are determined for samples stored at, respectively, the two lowest (4°C or 25°C) and the highest (50°C) temperature conditions. One selected example is illustrated in Fig. 1.

The mathematical bending point model can be formulated as follows:

$$Y_i=\beta_0+\beta_1 I_i t_i+\beta_2 I_i+\varepsilon_i \quad (1)$$

where Y_i is the percentage dissolution at time point i; I_i is the indicator or dummy variable ($I=1$ or 0 for the linear or the plateau part of the dissolution curve, respectively); $\beta_{0;1;2}$ are the linear least squares regression parameters; and ε_i is the residual error in the regression model at time point i.

Equation 1 can easily be rewritten as a function of the value of the dummy variable I:

$$I=1, \text{ or for the linear part of the curve,}$$
$$Y_i=(\beta_0+\beta_2)+\beta_1 t_i+\varepsilon_i \quad (2)$$

$$I=0, \text{ or for the plateau part of the curve,}$$
$$Y_i=\beta_0+\varepsilon_i \quad (3)$$

From Eqs. 2 and 3, it can be noticed that β_0 equals the percentage dissolution at the dissolution plateau level, whereas $(\beta_0+\beta_2)$ equals the intercept of the linear part of the bending point model. The slope of the linear part equals β_1. For experimental validation purposes, the null hypothesis $H_0:\beta_0+\beta_2=0$ versus $H_1:\beta_0+\beta_2\neq 0$ can be used to assess if the mean dissolution curve model goes through (0,0). For the example illustrated in Fig. 1, the intercept of the linear part is estimated as 0.2%, with a corresponding significance level of 0.8. Consequently, it is concluded that the dissolution curve model passes through the origin.

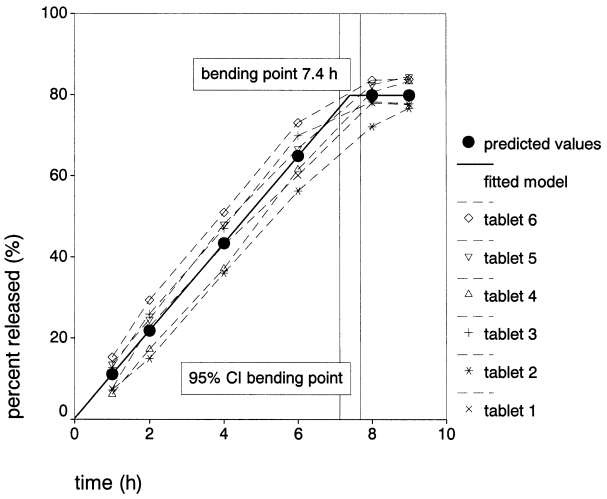

Figure 1. Selected dissolution experiment (batch 98L09 stored at 4°C) with plots of the six individual dissolution curves and an illustration of the fitted bending point model.

A typical phenomenon observed in most dissolution experiments used in this study is that the individual tablets show some systematic deviation from the mean dissolution profile. In other words, some individual dissolution curves are systematically above the mean profile, whereas others are systematically lower than the mean dissolution profile. This is also illustrated in Fig. 1. Other similar dissolution data studies presented in the literature (3,10) show the same behavior. This individual random "bias" for each tablet or between-tablet variability can easily be accounted for in the bending point model by including a random tablet effect in the model description. The extended bending point model for 1 tablet can be written as follows:

$$Y_{ij}=\beta_0+\beta_1 I_i t_i+\beta_2 I_i+\mu_j+\varepsilon_{ij} \quad (4)$$

where Y_{ij} is the percentage dissolution at time point i for tablet j, and μ_j is the bias effect attributed to tablet j. The extended bending point model that describes the mean dissolution becomes

$$Y_i=\beta_0+\beta_1 I_i t_i+\beta_2 I_i + 1/6(\mu_1+\mu_2+\cdots+\mu_6)+\varepsilon_{ij} \quad (5)$$

During parameterization of the model presented by Eq. 5, one of the μ_j effects should be set to 0 because it is redundant. In this case, tablet 6 was chosen as the reference tablet; thus, $\mu_6=0$. For

reasons of clearness, Eq. 5 can again be rewritten as a function of the value of the dummy variable I:

$$\begin{aligned} &I = 1, \text{ or for the linear part,} \\ &Y_i = (\beta_0 + \beta_2 + 1/6(\mu_1 + \cdots + \mu_5)) + \beta_1 t_i + \varepsilon_{ij} \end{aligned} \quad (6)$$

$$\begin{aligned} &I = 0, \text{ or for the plateau part,} \\ &Y_i = \beta_0 + 1/6(\mu_1 + \cdots + \mu_5) + \varepsilon_{ij} \end{aligned} \quad (7)$$

The bending point is defined as the point in time (h) at which Eqs. 6 and 7 have their intersection. Mathematically, the bending point ξ is defined as

$$\xi = -\beta_2/\beta_1 \quad (8)$$

The confidence information for ξ can be assessed using the delta method (11). It provides a simple approximate means of obtaining the standard error of a reparameterization without calculating the new information matrix. Applying the delta method to Eq. 8 results in

$$\sigma_\xi^2 = \left(\frac{\partial\xi}{\partial\beta_1}\right)^2 \sigma_{\beta_1}^2 + 2\left(\frac{\partial\xi}{\partial\beta_1}\right)\left(\frac{\partial\xi}{\partial\beta_2}\right)\sigma^2\{\beta_1, \beta_2\} + \left(\frac{\partial\xi}{\partial\beta_2}\right)^2 \rho_{\beta_2}^2 \quad (9)$$

where σ_ξ^2, $\sigma_{\beta_1}^2$, and $\sigma_{\beta_2}^2$ are the variance of ξ, β_1, and β_2, respectively; $\sigma^2\{\beta_1,\beta_2\}$ is the covariance between β_1 and β_2; $\partial\xi/\partial\beta_1$ is the partial derivative and equals β_2/β_1^2; and $\partial\xi/\partial\beta_2$ is the partial derivative and equals $-1/\beta_1$.

Finally, a 95% confidence interval for ξ can be constructed around the estimated $\xi \pm 2$ times the estimated standard error σ_ξ. For the example, in Fig. 1, this appropriate confidence interval is plotted on the graph.

Analysis of Drug Dissolution Data

Four different criteria to interpret the dissolution curves were considered: the bending point, the percentage dissolved at a fixed time point, the fitted Weibull parameters, and the area under the dissolution curve (AUC). Essentially, these criteria constituted a data reduction of 36 values (six tablets and six time points) into 3 (Weibull) or 1 (other criteria) values per dissolution experiment. The calculation details of the last three criteria are summarized as follows:

Percentage dissolved at a fixed time point: The time points 2, 4, and 6 h were selected. The mean and standard deviation were calculated from the measured values of the six tablets.

Fitted Weibull parameters: A Weibull model

$$Y = c*(1 - \exp(-a*t**b))$$

where Y is the percentage dissolved, t is the time (h), and a, b, and c are Weibull parameters, is fitted through the six dissolution profiles of each dissolution experiment using least-squares nonlinear regression. Asymptotic standard errors of the parameter estimates were calculated. Some authors (9) assume that the plateau value of the dissolution curve equals 100 per definition, and therefore set $c = 100$, consequently leaving only two Weibull parameters to be estimated from the data. In this particular study, experimental plateau values were found between 80% and 110% dissolution, being the main reason for incorporating the parameter c in the Weibull model.

AUC: The area under the dissolution curve for each tablet was calculated using the trapezoidal rule. The mean and standard deviations were calculated from the AUC values of the six tablets per experiment.

The relative standard deviation (RSD) for each of the four criteria was calculated for comparison purposes.

Data Processing

The statistical calculations, including the nonlinear parameter estimation for the Weibull model, were performed with the software SPSS® 9.0. The statistical bending point model used to describe a set of dissolution curves was implemented in SPSS 9.0, more particularly, using the general linear model (GLM) procedure. This yielded the parameter estimates of the bending point model, together with the related variance-covariance matrix. These data were read in an Excel® 2000 spreadsheet and further processed to yield the bending point estimate and its confidence information. The bending point method requires designation of whether the curve is (1) linear rising and (2) has reached a plateau. The assessment of these two requirements was also performed with the SPSS software using a syntax script in which the two statistical tests described above, were implemented. Currently, we are developing an application in Excel that performs automatically all necessary statistical tests and calculations related to the bending point determination.

For all statistical tests, a critical significance level of $\alpha = .05$ was chosen.

RESULTS AND DISCUSSION

Comparison of the Selected Dissolution Criteria

Here, emphasis is put on dissolution criteria that can be calculated from a single dissolution experiment (with preferably six or more tablets per experiment). Therefore, a number of strictly comparative criteria (such as the similarity factor f_2) (4) that are used to compare dissolution profiles (e.g., to compare a reference batch with a new batch) are outside the scope of this article.

Summary results of the different dissolution criteria applied to the experimental dissolution data are presented in Table 2. The RSD values are tabulated to make comparisons among the different criteria possible.

For all illustrated criteria, minor differences are noticed between the storage conditions 4°C and 25°C. However, all criteria except the Weibull parameters b and c show a clear discriminating effect between the storage conditions 4°C and 25°C on the one hand and the storage condition 50°C on the other. The RSDs of the bending point for the storage conditions 4°C and 25°C are remarkably lower (typically between 1% and 2%) than the corresponding values for the other criteria (typically between 3% and 15%). For the stress condition of 50°C, this difference is less remarkable.

The estimated standard errors and their related 95% confidence intervals of the bending points within one storage condition are more stable (or equal) compared to the other criteria (see Table 2). Further, the 95% confidence intervals for the bending points within one batch overlap more closely compared to the other criteria. For example, the AUC criterion for the storage condition 50°C shows a significant difference between batch 98L09 and batch 98L10, which is not considered very realistic or meaningful. More detailed analysis of the raw dissolution data (see Table 1) shows that, for instance, tablet 5 of batch 98L09 at storage condition 50°C reaches a clearly lower plateau value (around 80%), whereas tablet 2 reaches a clearly higher plateau value (around 115%) compared to the mean plateau (around 100%). This deviating behavior of a few tablets does have a pronounced effect on the estimated AUC value and its variability, for instance; however, the calculated bending point is insignificantly affected by these individual tablet variations within the considered batch. This illustrates the robustness of the bending point.

The criterion "mean dissolution after x hours" is by far the simplest; however, it is not considered very informative, and it is based on a very limited subset of the available dissolution data. This is in correspondence with recent literature (8,9), in which the model-based approaches are considered a better tool for the characterization and comparison of dissolution profiles. The Weibull method has the advantage that it yields three parameter estimates (a, b, and c); however, only the parameter a shows some discriminating power between dissolution curves of samples stored at different temperatures. Moreover, the physical interpretation of the Weibull parameter a is not straightforward. The AUC criterion was found to give similar information compared to the bending point; however, the AUC was found to be more sensitive to intertablet variations and more heavily determined by the absolute plateau dissolution value. Furthermore, there was a mathematical relationship between these two criteria: an increase $\Delta\xi$ in the bending point value theoretically corresponded with a decrease in AUC, or $\Delta\text{AUC} = -1/2\beta_0 * \Delta\xi$.

The a priori information included in the bending point model (see the two conditions at the beginning of this section) is the highest of all criteria studied. This may result in the lowest RSD values observed. Moreover, it is the only model that incorporates the "bias" effect μ_j of individual tablets. For the dissolution data presented in this article, the bending point is considered the best choice for an appropriate dissolution criterion. However, in case the plateau and linearity assumptions would not be valid, other criteria could possibly be preferred.

A supplementary interesting property of the bending point is that it has a particular physical interpretation, being the moment in time at which the tablet is completely dissolved. This aspect is of particular interest for slow-release buccal tablets because the in vivo behavior of the tablet is mainly determined by its physical properties. Preliminary experiments indicate that the in vivo residence time of the tablet in the mouth well corresponds with the bending point determined in vitro. This is a promising function of the in vitro–in vivo relationship that will be established in a future stage.

Table 2

Means, Standard Deviations (SDs) (or Standard Errors [SEs]), Relative Standard Deviations (RSDs) and 95% Confidence Intervals (CIs) for Different Dissolution Criteria Applied to the Data of Table 1

	4°C			25°C			50°C		
	98L08	98L09	98L10	98L08	98L09	98L10	98L08	98L09	98L10
Bending point									
Value (h)	7.7	7.4	7.6	7.0	7.0	7.3	3.3	2.8	3.1
SE (h)	0.15	0.14	0.10	0.07	0.11	0.07	0.20	0.18	0.15
RSD (%)	1.9	1.9	1.3	1.0	1.6	1.0	6.1	6.4	4.8
95% CI (h)	7.4–8.0	7.1–7.9	7.4–7.8	6.9–7.1	6.8–7.2	7.2–7.4	2.9–3.7	2.4–3.2	2.8–3.4
Dissolution 2 h									
Mean value (%)	17.7	22.5	25.0	26.7	25.7	27.3	63.2	76.3	61.5
SD (%)	2.7	5.4	2.0	1.7	4.7	1.4	8.3	4.0	2.8
RSD (%)	15.4	24.2	8.0	6.4	18.2	5.2	13.1	5.2	4.6
95% CI (%)	15.5–19.9	18.0–26.9	23.3–26.6	25.3–28.1	21.9–29.6	26.2–28.5	55.8–70.6	73.0–79.5	59.1–63.8
Dissolution 4 h									
Mean value (%)	43.7	43.7	46.4	51.6	50.0	49.5	97.1	100.9	88.4
SD (%)	3.0	6.1	3.0	1.6	4.4	2.9	4.0	9.8	6.7
RSD (%)	6.8	13.9	6.6	3.1	8.7	5.9	4.2	9.7	7.5
95% CI (%)	41.2–46.1	38.7–48.6	43.9–48.9	50.3–52.9	46.5–53.6	47.1–51.9	93.5–100.7	92.9–108.9	83.0–93.9
Dissolution 6 h									
Mean value (%)	68.6	64.6	67.2	74.3	74.9	72.4	94.1	100.5	89.4
SD (%)	5.7	6.4	4.4	3.4	1.8	3.4	3.1	7.5	3.5
RSD (%)	8.3	9.9	6.5	4.6	2.4	4.7	3.3	7.5	4.0
95% CI (%)	63.9–73.2	59.3–69.8	63.7–70.8	71.5–77.1	73.4–76.3	69.6–75.2	91.3–96.8	94.4–106.6	86.5–92.2
Weibull a									
Value	0.06	0.10	0.10	0.13	0.12	0.12	0.50	0.59	0.48
SE	0.006	0.011	0.012	0.008	0.009	0.008	0.045	0.055	0.028
RSD (%)	10.0	11.3	12.2	6.1	7.8	6.6	9.1	9.3	5.9
95% CI	0.05–0.07	0.08–0.12	0.08–0.12	0.12–0.15	0.10–0.14	0.11–0.14	0.41–0.59	0.48–0.70	0.42–0.53
Weibull b									
Value	1.56	1.28	1.12	1.28	1.32	1.19	1.37	1.25	1.34
SE	0.108	0.133	0.091	0.070	0.090	0.075	0.157	0.169	0.097
RSD (%)	6.9	10.4	8.1	5.5	6.8	6.3	11.5	13.5	7.2
95% CI	1.34–1.78	1.01–1.55	0.94–1.30	1.14–1.42	1.14–1.50	1.04–1.34	1.06–1.68	0.91–1.59	1.15–1.53
Weibull c									
Value (%)	107	101	127	98	101	110	94	102	90
SE (%)	7.4	12.8	20.3	4.3	5.9	8.4	1.6	1.9	1.0
RSD (%)	6.9	12.7	16.0	4.4	5.9	7.6	1.7	1.8	1.1
95% CI (%)	92–122	75–127	86–168	90–107	89–113	93–127	90–97	98–106	88–92
AUC									
Mean value (h*%)	436	420	448	480	477	474	698	769	663
SD (h*%)	23	42	25	14	18	17	32	48	14
RSD (%)	5.2	9.9	5.5	3.0	3.7	3.6	4.6	6.3	2.1
95% CI (h*%)	417–454	386–454	427–468	468–491	463–492	460–488	669–727	729–808	652–675

CI, confidence intervals; RSD, relative standard deviation; SD, standard deviation; SE, standard error.

CONCLUSION

A novel bending point criterion was developed and compared with a number of existing criteria for the interpretation of dissolution profiles. The bending point model is based on two rather strict assumptions, the recording of the dissolution curve until its plateau level and a linear dissolution rate in the first part of the dissolution curve. The model also includes a bias effect for individual tablets to

take into account small tablet variations within a single dissolution experiment.

The RSD values of the bending point are typically between 1% and 5%, which are considerably lower than the corresponding values of the other criteria (typically between 3% and 15%). The estimated bending points for a particular storage condition but different batches were not significantly different, whereas the other criteria often had significant but meaningless differences between batches. The estimated variability of the bending point was also found more stable compared to the other criteria investigated.

The bending point criterion is considered robust and stable for the characterization of certain dissolution profiles. Moreover, the bending point has a particular physical interpretation that is helpful in the framework of the slow-release application of this buccal tablet.

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