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On the Characteristics of the FDA's Similarity Factor for Comparison of Drug Dissolution

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ABSTRACT

The characteristics of FDA's similarity factor (f_2) are investigated and compared with those of the time-series approach proposed by Chow and Ki for the comparison of dissolution profiles. The results indicate FDA's similarity factor simply reflects the overall average difference in percent dissolved of drug, regardless of the different pattern of dissolution. It should be noted, however, that the percent dissolved data in the profile are highly correlated time-series data; they are not the independent variables that the FDA's method assumed. Moreover, the asymptote is usually reached within 45 minutes of dissolution for most of the immediate release solid dosage form products. A high f_2 value can be manipulated if one includes several more data points at the asymptote to overcome the large differences observed in 15 to 45 minutes dissolution. Thus, the true difference in dissolution characteristics of the two products may be distorted. Although the f_2 method has the advantage of simplicity, it lacks strict statistical justification. On the other hand, the time-series approach proposed by Chow and Ki is much more powerful in discerning differences in dissolution pattern between two drug products. However, Chow and Ki's method does not consider cases with a declined cumulative dissolution profile.

Key words: **similarity factor, Chow and Ki's time-series approach, dissolution profiles comparison.**

INTRODUCTION

The bioavailability of drug products is essential for the safety and effectiveness of drug therapy. However, due to the expense of human testing, dissolution profiles comparisons have been proposed for the minor changes in manufacturing. Recently, the United States Food and Drug Administration (FDA) released "SUPAC IR Guidance"[(1)] (Scale Up and Post Approval Change for Immediate Release solid dosage forms). In section VII In Vitro Dissolution, the

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similarity factor (f_2) is introduced[2]. However, the theoretical basis of the similarity factor is rather ambiguous. This report demonstrates and discusses the characteristics of the similarity factor and the different results obtained with Chow and Ki's time-series approach[3] using a set of real dissolution data.

MATERIALS AND METHODS

I. *Data Set*

A set of real dissolution data (two test batches of gemfibrozil 500 mg tablets in pH 6.8 medium using USP type II, 50 rpm) is listed in Table 1.

II. *FDA's Similarity Factor*

FDA suggests that dissolution profiles may be compared using equation (1), which defines a similarity factor (f_2). R_t and T_t are the percent dissolved data at each time point, and n is the number of paired dissolution data. An f_2 value between 50 and 100 suggests the two dissolution profiles are similar.

$$f_2 = 50LOG_{10}([1+\frac{1}{n}\sum_{t=1}^{n}(R_t - T_t)^2]^{-0.5}\text{x}100) \quad ....(1)$$

III. *Chow and Ki's Time-series Approach*

Chow and Ki[3] proposed a time-series approach to compare two dissolution profiles in 1997. In this approach equivalence limits for similarity are based on the amount of dissolved drug as specified in the USP (Q value). The test drug product is considered to have a similar mean dissolution rate to the reference drug product if the 95% (or 90%) confidence interval of the mean ratio of dissolution rates (L, U) falls within (Q-δ, Q+δ), where δ is the meaningful difference. Briefly, let X_{ti} and Y_{ti} denote the percent dissolved of the reference and the test products observed from the ith dissolution medium (ith location of dissolution vessel) at time t, respectively, and i=1...n, t=1...T. Then the ratio of dissolution results at location i and time t, defined as $R_{ti} = Y_{ti}/X_{ti}$ is a measure of the relative dissolution rate. Assuming R_{ti} can be described by the following autoregressive time-series model:

$$R_{ti} = \gamma_{ti} + \phi_i(R_{(t-1)i} - \gamma_{(t-1)i}) + \varepsilon_{ti}$$

Then, according to Chow and Ki[3], the (1-α)x100 % confidence interval of the ratio of dissolution results (L, U) can be written as follows.

$$L = \hat{\gamma} - z(1-\alpha/2)(\sigma\hat{\gamma} + \tau) \quad U = \hat{\gamma} + z(1-\alpha/2)(\sigma\hat{\gamma} + \tau)$$

where $z(1-\alpha/2)$ is the $(1-\alpha/2)$th percentile obtained from the normal distribution.

$$\hat{\tau}^2 = \frac{1}{nT-1}\sum_{i=1}^{n}\sum_{t=1}^{T}(R_{ti} - \bar{R})^2 - \frac{1}{n(T-1)}\sum_{i=1}^{n}\sum_{t=1}^{T}(R_{ti} - \bar{R}_i)^2 \quad ....(2)$$

$$\hat{\gamma} = \frac{1}{n}\sum_{i=1}^{n}\bar{R}_i \qquad \sigma_{\hat{\gamma}} = (\frac{1}{n^2}\sum_{i=1}^{n}Var(\bar{R}_i))^{\frac{1}{2}}$$

$$Var(\bar{R}_i) = \frac{\psi_i^2}{T}\{1 + 2\sum_{k=1}^{T-1}\frac{T-K}{T}\phi_i^k\} + \frac{1}{T}\tau^2$$

$$\hat{\psi}_i^2 = \frac{1}{T-1}\sum_{t=1}^{T}(R_{ti} - \bar{R}_i)^2 \qquad \bar{R}_i = \frac{1}{T}\sum_{t=1}^{T}R_{ti}$$

$$\hat{\phi}_i = \frac{\sum_{t=1}^{T-1}(R_{ti} - \bar{R}_i)(R_{(t+1)i} - \bar{R}_i)}{\sum_{t=1}^{T}(R_{ti} - \bar{R}_i)^2}$$

RESULTS AND DISCUSSION

I. *Characteristics of Similarity Factor (f_2)*

The FDA's definition of the symbols R_t and T_t in equation (1) is somewhat ambiguous. R_t and T_t may respectively represent the mean values of the percent dissolved data at time t for the twelve units of reference and test products, regardless of their variances. On the other hand, they also may more reasonably be taken as individual percent dissolved data at time t of the reference and test products in the same dissolution vessel. Equation (1) yields f_2=100 when $\Sigma(R_t-T_t)^2$=0. This means that the dissolution profiles for the reference and test products overlap and are identical. Similarly, f_2=50 when $1/n[\Sigma(R_t-T_t)^2]$=99. This is the acceptable limit of mean squares of the difference for similar dissolution rates. In other words, if the mean squares of the difference of percent dissolved data are not larger than 99 or the mean difference in percent dissolved data is not larger than $(99)^{1/2}$=9.95%, then the f_2 value will not be less than 50 and the similarity of the two dissolution

profiles can be concluded. The Guidance document also recommends that the multi-point dissolution profile be performed in the application medium at 15, 30, 45, 60, and 120 minutes until either 90 percent of the drug from the drug product is dissolved or an asymptote is reached[4]. Hence, there are usually five time point data in a dissolution profile. In general, $\Sigma^5_{t=1}$ $(R_t-T_t)^2 \leq (99x5)$ or 495 is mandatory for $f_2 \geq 50$. A mean difference at any time point larger than $(495)^{1/2}$ or 22.25% will lead to $f_2<50$. For the data set in Table 1, the 95% confidence intervals of the mean difference are 10.9/16.6 (15 min), 8.1/11.7 (30 min) and 6.8/8.4 (45 min). Table 2 shows the paired differences in percent dissolved data. It is evident that three of the paired dissolution profiles are not similar because the f_2 value for each of these paired profiles is less than 50 (pair codes 8, 11 and 12). However, it is intriguing to see that the overall f_2 value for the 12 paired profiles calculated with equation (1) is 51.4, which marginally exceeds the lower acceptable limit of FDA's similarity criteria. The results indicate that the FDA's similarity factor simply reflects the overall average difference in 12 paired profile data, regardless of the difference of the dissolution pattern between the reference and test products. In addition, it should be noted that the percent dissolved data in the profile are highly correlated time series data; they are by no means independent variables. Therefore, the assumptions that underlie the FDA's f_2 method obviously are not reflected in the real situation. Moreover, the asymptote is usually reached within 45 minutes of dissolution for most of the immediate release solid dosage form products. We have surveyed 293 items compiled in the USP/NF XXIII/XVIII and found only about 2% of the immediate release products that reach their asymptote later than 45 minutes of dissolution. Furthermore, it is not uncommon for small differences in percent dissolved to be observed after 45 minutes dissolution between two different brand products. A large f_2 value can be manipulated if one includes several more data points near the asymptote to overcome any large differences observed at 15 to 45 minutes. Because the f_2 value is calculated from the mean squares of the difference of percent dissolved data, the same f_2 value is obtained regardless which of the two drugs in a pair is designated the reference. For instance, the f_2 value will be still 51.4, even if the dissolution data are reversed for the reference and test products at pair code Nos. 8, 9, and 10. Thus, the true difference in dissolution characteristics of the two products may be distorted and misinterpreted. Liu et al.[5] criticized the FDA's f_2 approach in that the complexity of the form of the distribution of f_2 prevents one from finding its variance and the confidence interval of the mean. In addition, the results of simula-

Table 1. Percent dissolved data

Dissolution Time (min)	15	30	45	60	120
Code No.	Reference Product				
1	31	45	58	75	80
2	37	45	65	78	82
3	38	48	70	80	85
4	32	36	67	76	86
5	33	42	69	77	88
6	37	45	72	82	89
7	29	42	64	73	81
8	33	43	71	84	90
9	33	52	74	80	90
10	32	46	66	76	84
11	36	53	65	70	81
12	33	48	68	80	85
Code No.	Test Product				
1	25	33	50	70	80
2	22	35	60	73	82
3	26	38	63	75	85
4	19	34	59	71	83
5	18	32	61	72	85
6	21	36	65	78	87
7	22	33	58	67	79
8	17	32	62	77	89
9	21	40	66	75	85
10	19	37	59	70	80
11	13	31	57	70	81
12	16	35	58	75	83

Table 2. Differences between percent dissolved and f_2 values

Time (min)	15	30	45	60	120	Mean $(R_t-T_t)^2$	f_2
Pair Code 1	6	12	8	5	0	53.8	56.5
2	15	10	5	5	0	75.0	53.0
3	12	10	7	5	0	63.6	54.7
4	13	2	8	5	3	54.2	56.5
5	15	10	8	5	3	84.6	51.7
6	16	9	7	4	2	81.2	52.1
7	7	9	6	6	2	41.2	59.4
8	16	11	9	7	1	101.6	49.7
9	12	12	8	5	5	80.4	52.2
10	13	9	7	6	4	70.2	53.7
11	23	12	8	0	0	135.4	46.6
12	17	13	10	5	2	117.4	48.2
Mean	13.8	10.7	7.6	4.9	1.7	79.9	52.9
SD	4.5	1.4	1.3	1.7	1.7	27.3	3.7

The overall f_2 value for the two products calculated by Eq.1 is 51.4.

Table 3. Chow and Ki's time-series approach, global and local similarity tests

Global Similarity Test

Acceptable Criteria for Similarity under Q=85.1%
δ=9.95%: 79.1/126.5
95% confidence interval of the ratio of the mean dissolution results between two dissolution profiles: 78.2/88.6
90% confidence interval of the ratio of the mean dissolution results between two dissolution profiles: 79.0/87.7
Hence, the two dissolution profiles are not globally similar based on 95 or 90% confidence interval

Local Similarity Test

Time (min)	Mean (%)	95% CI		90% CI	
		Lower limit(%)	Upper limit(%)	Lower limit(%)	Upper limit(%)
15	59.5	56.2	63.6 [a]	56.8	63.0 [a]
30	76.9	73.3	80.7 [a]	73.9	80.1 [a]
45	88.7	84.9	92.4	85.5	91.8
60	93.8	89.9	97.4	90.5	96.8
120	97.9	93.9	101.4	94.5	100.8

CI: confidence interval.
[a]: not similar based on Q=85.1%, δ=9.95%.

tion study made by Liu et al.[5] indicate that f_2 is too liberal in concluding similarity between two dissolution profiles. The FDA's f_2 method may be simple, but it lacks strict statistical justification. Not enough information is available to support the validity of the method.

II. *Characteristics of Chow and Ki's Approach*

Chow and Ki's time-series approach determines equivalence in two dissolution profiles if the ratio of dissolution rates is within some equivalence limits with certain assurance (e.g. 95% or 90% confidence). Global similarity can be concluded if two dissolution profiles are similar across all time points; whereas local similarity can be established if two profiles are only similar at some specific time points. Table 3 depicts the results of the global and local similarity tests by Chow and Ki's approach with the same data set used previously for f_2 value calculation. The results suggest that the two dissolution profiles are not globally similar when the mean percent dissolved data of the reference product at the last measured point (85.1%) is used as the Q value and the meaningful difference is 9.95% (based on FDA's f_2 principle). The local similarity test shows that the two dissolution profiles are not similar at time 15 and 30 min. Our experiences in the analysis of dissolution profiles, based on the real data submitted to the DOH (Department of Health, Taiwan) by pharmaceutical companies for drug products registration, reveal that Chow and Ki's approach can discriminate more powerfully than the f_2 method between two dissolution profiles.

However, the interpretation of the results would be difficult in cases of a declined cumulative dissolution profile. The declination of a cumulative dissolution profile may result from drug hydrolysis or reduced solubility (drug precipitation) during the dissolution test. In fact, Chow and Ki's approach does not consider the negative τ^2 values (equation 2) that would result in a declined dissolution profile. The declination of dissolution profiles after 30 min of dissolution is not uncommon for drugs that are the salts of a weak acid or weak base (e.g. the solubility of tetracycline HCl in water drastically decreases on standing due to the precipitation of the tetracycline base). Hence, further modification of Chow and Ki's approach will be required.

In conclusion, there is still no reasonable and reliable method available to assess the similarity of drug dissolution profiles. In addition, since the quantitative correlation between the difference in dissolution rate and the difference in bioavailability of drug products has yet to be established, the use of SUPAC as a substitute for in vivo testing should always be carefully justified.

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美國FDA的溶離曲線類同度的特性

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摘 要

藥品的生體可用率特性爲確保藥物治療之有效性及安全性之重要品質，各國皆經由法規之制訂加以嚴格管理。然而對同一廠商在優良藥品製造規範（cGMP）之管制下所生產的不同批次之同一製劑或生產配方或產程上有些微次要的變更者，允許以溶離曲線之比對代替昂價費時的人體試驗作爲品質確保的方便方法。美國FDA公布溶離曲線比對的基準，但所用之類同度之意義曖昧，被認爲有統計學上及藥劑學上之疑慮。本報告針對FDA之類同度以及Chow and Ki所提倡的時間數列解析法，以實例加以剖析檢討。結果顯示FDA類同度法雖然簡易，但不能反映溶離曲線眞實的差異。時間數列解析法雖然比較靈敏能區別溶離曲線形的差異性，但對溶解度隨溶離時間減少之弱酸或弱鹼鹽類藥物之溶離曲線之比對無法使用。在缺少合理可靠的溶離曲線比對方法以及溶離特性和生體可用率尚無明確的相關性之狀態下，以簡陋的FDA類同度作爲溶離曲線的比對方法而省略人體生體可用率及生體相等性試驗，必須相當的謹慎。

關鍵詞：溶離曲線類同度，時間數列解析法。