

Refinement of Lower Acceptance Value of the Similarity Factor f_2 in Comparison of Dissolution Profiles

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Abstract

Dissolution testing has become an essential tool in the pharmaceutical industry at various stages of development, manufacturing and marketing. For the comparison of dissolution profiles, similarity factor f_2 is gaining popularity due to its recommendation by various regulatory committees. Dissolution profiles are considered similar if the calculated f_2 value is between 50 and 100. In our opinion, this acceptance limit might not be correctly defined. This article presents the reasons for the same and a new equation to define the lower acceptance limit for different data sets. It is proposed that regulatory agencies should actively consider the revision of the lower acceptance value for f_2 .

Introduction

Over the last quarter century, dissolution testing has emerged as a highly valuable in-vitro test to characterize the performance of a dosage form. The popularity of dissolution testing is based on the fact that solubilization of a drug in gastrointestinal fluid is a prerequisite for the drug to be absorbed and available to the systemic circulation. The dissolution testing is performed as a relatively fast and inexpensive technique to evaluate pharmaceutical dosage forms before they are tested in clinical trials. It is prudent to have extensive dissolution data to maximize the chances for success in bioavailability testing in humans.

Dissolution testing can be used: (1) to detect the influence of critical formulation and manufacturing variables in Formulation & Development and Research & Development; (2) to assist in selection of a best formulation; (3) to check the changes during stability studies; (4) to establish final dissolution specifications for the pharmaceutical dosage form; (5) to develop IVIVC [1]; (6) as a quality control tool; and (7) to establish the similarity of pharmaceutical dosage forms, for which composition, manufacturing site, scale of manufacture, manufacturing process and/or equipment may have changed within defined limits [2,3].

Dissolution testing can be used as a surrogate for bioavailability and bioequivalence under some conditions such as minor formulation or equipment changes, multiple strengths of the same drug product, manufacturing site changes, batch scale-up, and justifying dissolution specification range [4]. In some cases, bioavailability needs to be demonstrated only 'if the product fails to achieve adequate dissolution when compared to a standard' [5]. The US FDA requires that dissolution data

be included for a new drug application (NDA) and an abbreviated new drug application (ANDA) submission for bioequivalence review.

To the pharmaceutical researchers involved in dissolution testing of dosage forms, the similarity factor f_2 is not unknown. After introduction of this factor by Moore and Flanner [6], it has been adopted by the Center for Drug Evaluation and Research (US FDA) and by Human Medicines Evaluation Unit of The European Agency for the Evaluation of Medicinal Products (EMA) as a criterion for the assessment of the similarity between two dissolution profiles. It is included in various guidance documents [2, 3, 7-9].

The similarity factor f_2 as defined by FDA and EMA is a logarithmic reciprocal square root transformation of one plus the mean squared (the average sum of squares) differences of drug percent dissolved between the test and reference products:

$$f_2 = 50 \times \log \left\{ \left[1 + \frac{1}{n} \sum_{t=1}^n |R_t - T_t|^2 \right]^{-0.5} \times 100 \right\} \quad (1)$$

where n is the number of dissolution time points, and R_t and T_t are the reference and test dissolution values (mean of at least 12 dosage units) at time t .

When the two dissolution profiles are identical, $f_2 = 50 \times \log(100) = 100$, and when the dissolution of one product (test or reference) is completed before the other begins, $f_2 = 50 \times \log \left\{ \left[1 + 1/n(100)^2 \right]^{-0.5} \times 100 \right\} = -0.001$, which can be rounded to 0. Thus the value of f_2 ranges from 0 to 100. A higher f_2 value indicates closeness between the two dissolution profiles. The equation of f_2 is only applicable in comparing curves in which the aver-

age difference between R and T is less than 100 [6]. In other words, the amount of drug released shall be expressed in percent.

Shah et al [10] reported that an average difference of no more than 10% at any sampling time point between reference and test products may be acceptable. The authors further stated that when this 10% average absolute difference is substituted in the equation, f_2 becomes 50. As per current guidance documents, two dissolution profiles are considered 'similar' when the f_2 value is between 50 and 100. The rationale for providing this acceptable range is that in a real life situation, it is not expected to have f_2 value be 100 even when the two dissolution profiles are generated from the same batch due to intra-batch variation.

As per current understanding, if the percent drug released from reference product is 15 at time t, a range of 5 to 25 is permissible for the test product at the same time point. In our opinion, the current lower limit of f_2 is very liberal, especially for sustained release (SR) formulations. This can be explained by taking two hypothetical examples. Consider two SR release profiles, one is a 12 hr zero-order profile and the other is a 24 hr zero-order profile as the reference release profiles (Table 1 and 2). Table 1 and 2 also show the percent deviation allowed, as per the current understanding. One would find that this percent deviation is very high. For example, for the 12 hr zero-order release profile up to $\pm 40\%$ and for the 24 hr zero-order release profile up to $\pm 80\%$ deviation is allowed in the initial phase (i.e. up to 3 hr). This is very critical especially for the SR formulations of the drug with narrow therapeutic index.

In bioequivalence studies of SR products, one of the objectives is to document that the product does not release the drug too rapidly (dose dump) [11]. Due to many reasons, the possibility of deviation in in-vivo testing is very high as compared to that in in-vitro testing. Despite this possibility, the

Table 1. Percent deviation allowed for a 12 hr zero-order released profile as per current theory.

Time (hr)	Cumulative percent drug released Reference (R)	Test 1 (R + 10)	Test 2 (R - 10)	Percent deviation allowed
1	8.33	18.33	-1.67	120.0
2	16.67	26.67	6.67	60.0
3	25.00	35.00	15.00	40.0
4	33.33	43.33	23.33	30.0
5	41.67	51.67	31.67	24.0
6	50.00	60.00	40.00	20.0
7	58.33	68.33	48.33	17.1
8	66.67	76.67	56.67	15.0
9	75.00	85.00	65.00	13.3
10	83.33	93.33	73.33	12.0
11	91.67	101.67	81.67	10.9
12	100.00	110.00	90.00	10.0

$f_2 = 50$ for Reference versus Test 1
 $f_2 = 50$ for Reference versus Test 2
 Note: Absolute percent difference allowed at all time is equal to 10

current allowable limit for the bioequivalence study is 80 – 125% [12].

If 10% deviation with respect to the dissolution profile of reference product is to be allowed for dissolution profiles to be similar, the lower limit for f_2 value is to be calculated as shown in Table 3 and 4. The f_2 values were calculated using equation 1. The generalized equation to estimate the lower acceptable value of f_2 (f_{2LX}) is shown below where X is the percent deviation (e.g. 2, 5, 10, etc).

$$f_{2LX} = 50 \times \log \left\{ \left[1 + \frac{1}{n} \sum_{t=1}^n \left| R_t - \left(R_t \pm \frac{X}{100} R_t \right) \right|^2 \right]^{0.5} \times 100 \right\} \quad (2)$$

The lower acceptable f_2 (f_{2L10}) values were calculated for a large number of dissolution data sets generated in our laboratory as well as for published work [13-17]. It was found that the f_{2L10} value was dependent on individual data set, which indicates that no general acceptable limit can be suggested. Table 5 shows the values of f_2 and f_{2LX} for the 12 hr and 24 hr zero-order release profiles. If one intends to suggest a lower acceptable value of f_2 for 12 hr or 24 hr zero-order release profile, a value of 60 may be suggested. This value is 20%

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higher than the currently used value of 50. We also would like to point out that, as per current theory, instead of 10%, approximately 16% deviation is allowed between two dissolution profiles to be similar. The currently proposed liberal approach widens the acceptance criteria and may inadvertently lead to the declaration of similarity of dissolution profiles which otherwise are quite dissimilar.

SUPAC-MR guidance states that the average difference at any dissolution time point between test and reference mean profiles should not exceed 15% [3]. According to current theory, the f_2 value of 50 allows more than 15% deviation at many time points for the 12 hr and 24 hr zero-order release profiles. In other words, the current lower acceptable limit of f_2 value (i.e. 50) violates the

SUPAC – MR guideline.

It is also important to note that as per current theory, a negative value for percent drug released is encountered for the test product (Table 1 and 2), which is practically impossible. This situation, however, is not encountered in the proposed method to calculate lower limit of f_2 .

Conclusion

A wide range of methods is available for the comparison of dissolution profiles. The method proposed by Moore and Flanner is most popular because it is recommended in the US FDA and the EMEA guidance documents. In our opinion, the lower acceptance limit for the f_2 value is not properly set. A new concept for finding the acceptable

limit for the f_2 value and an equation to calculate it has been proposed. We would like to bring the kind notice of various regulatory committees to redefine the current acceptance limit of the similarity factor f_2 . Pharmaceutical formulators may consider the theory suggested in this article while making decisions regarding similarity of border line cases.

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Table 2. Percent deviation allowed for a 24 hr zero-order released profile as per current theory

Time (hr)	Cumulative percent drug released Reference (R)	Test 1 (R + 10)	Test 2 (R - 10)	Percent deviation allowed
1	4.17	14.17	-5.83	240.0
2	8.33	18.33	-1.67	120.0
3	12.50	22.50	2.50	80.0
4	16.67	26.67	6.67	60.0
5	20.83	30.83	10.83	48.0
6	25.00	35.00	15.00	40.0
7	29.17	39.17	19.17	34.3
8	33.33	43.33	23.33	30.0
9	37.50	47.50	27.50	26.7
10	41.67	51.67	31.67	24.0
11	45.83	55.83	35.83	21.8
12	50.00	60.00	40.00	20.0
13	54.17	64.17	44.17	18.5
14	58.33	68.33	48.33	17.1
15	62.50	72.50	52.50	16.0
16	66.67	76.67	56.67	15.0
17	70.83	80.83	60.83	14.1
18	75.00	85.00	65.00	13.3
19	79.17	89.17	69.17	12.6
20	83.33	93.33	73.33	12.0
21	87.50	97.50	77.50	11.4
22	91.67	101.67	81.67	10.9
23	95.83	105.83	85.83	10.4
24	100.00	110.00	90.00	10.0

$f_2 = 50$ for Reference versus Test 1
 $f_2 = 50$ for Reference versus Test 2
 Note: Absolute percent difference allowed at all time is equal to 10

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Table 3. Calculation of lower acceptable limit of f_2 value for a 12 hr zero-order release profile

Time (hr)	Cumulative percent drug released		
	Reference (R)	Test 1 (R + 10% of R)	Test 2 (R - 10% of R)
1	8.33	9.17	7.50
2	16.67	18.33	15.00
3	25.00	27.50	22.50
4	33.33	36.67	30.00
5	41.67	45.83	37.50
6	50.00	55.00	45.00
7	58.33	64.17	52.50
8	66.67	73.33	60.00
9	75.00	82.50	67.50
10	83.33	91.97	75.00
11	91.67	100.83	82.50
12	100.00	110.00	90.00

$f_2 = 60.33$ for Reference versus Test 1
 $f_2 = 60.33$ for Reference versus Test 2

Table 4. Calculation of lower acceptable limit of f_2 value for a 24 hr zero-order release profile

Time (hr)	Cumulative percent drug released		
	Reference (R)	Test 1 (R + 10% of R)	Test 2 (R - 10% of R)
1	4.17	4.58	3.75
2	8.33	9.17	7.50
3	12.50	13.75	11.25
4	16.67	18.33	15.00
5	20.83	22.92	18.75
6	25.00	27.50	22.50
7	29.17	32.08	26.25
8	33.33	36.67	30.00
9	37.50	41.25	33.75
10	41.67	45.83	37.50
11	45.83	50.42	41.25
12	50.00	55.00	45.00
13	54.17	59.58	48.75
14	58.33	64.17	52.50
15	62.50	68.75	56.25
16	67.67	73.33	60.00
17	70.83	77.92	63.75
18	75.00	82.50	67.50
19	79.17	87.08	71.25
20	83.33	91.67	75.00
21	87.50	96.25	78.75
22	91.67	100.83	82.50
23	95.83	105.42	86.25
24	100.00	110.00	90.00

$f_2 = 60.96$ for Reference versus Test 1
 $f_2 = 60.96$ for Reference versus Test 2

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Table 5. Calculated f_2 and f_{2LX} values for 12 and 24 hr zero-order release profiles at different percent deviation.

Percent deviation (X)	f_2	f_{2LX} (12 hr zero-order release profile)	f_{2LX} (24 hr zero-order release profile)
0	100.0	100.0	100.0
2	82.5	90.0	90.4
5	64.6	74.6	75.2
10	49.9	60.3	61.0
15	41.1	51.7	52.3
20	34.9	45.5	46.1

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