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Mathematical evaluation of similarity factor using various weighing approaches on aceclofenac marketed formulations by model-independent method

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The US Food and Drug Administration's (FDA's) guidance for industry on dissolution testing of immediate-release solid oral dosage forms describes that drug dissolution may be the rate limiting step for drug absorption in the case of low solubility/high permeability drugs (BCS class II drugs). US FDA Guidance describes the model-independent mathematical approach proposed by Moore and Flanner for calculating a similarity factor (f_2) of dissolution across a suitable time interval. In the present study, the similarity factor was calculated on dissolution data of two marketed aceclofenac tablets (a BCS class II drug) using various weighing approaches proposed by Gohel et al. The proposed approaches were compared with a conventional approach ($W = 1$). On the basis of consideration of variability, preference is given in the order of approach 3 > approach 2 > approach 1 as approach 3 considers batch-to-batch as well as within-samples variability and shows best similarity profile. Approach 2 considers batch-to batch variability with higher specificity than approach 1.

1. Introduction

Dissolution test for oral solid dosage forms was first introduced in the United States Pharmacopoeia (USP) 18 in 1969. The rational behind this test is that a drug should be appropriately dissolved within the gastrointestinal tract (GIT) in order to be absorbed. Dissolution hence has become the most important test to determine product quality and drug release behavior. Dissolution testing can be used: (1) to detect the influence of critical formulation and manufacturing variables in formulation and development and research and 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 (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 (Dressman et al. 1998; USFDA guidelines 1997; Amidon et al. 1995; SUPAC guidelines 1997).

The dissolution profile should be compared by the model-independent method proposed by Moore and Flanner (Shah et al. 1989; Moore et al. 1996).

$$f_2 = 50 \cdot \log \left\{ \left[1 + (1/n) \sum_{t=1}^{n} W(Rt - Tt)^2 \right]^{-0.5} \cdot 100 \right\} \quad (1)$$

The FDA guideline for industry allows the use of mean data and recommends that the percent coefficient of variation at an earlier time point (for example, 15 min) should not be higher than 20%, and at other time points not higher than 10%. Generally, f_1 values up to 15 (0–15) and f_2 values greater than 50 (50–100) ensure or equivalence of the two curves. A higher f_2 value indicates closeness between the two dissolution profiles.

The variability in the dissolution data may be attributed to human errors, equipment related errors, or formulation-related factors. Bartoszynski et al. (2001) pointed out that the procedure currently used by the FDA involves calculation of the mean amount dissolved at each time interval and comparison of the two mean curves considering optional weight as one. This approach ignores all of the variability within sets of profiles. The conventional approach for f_2 does not take into account the within-batch variability or the correlation between data (Adams et al. 2001; Sarandasa et al. 2001).

Gohel et al. (2005) provide a meaningful resolution of this issue by introducing a weight based on variability. The proposed approaches of considering weight, as it considers batch-to-batch as well as within-samples variability, evoke new interest in the area of comparison of dissolution profiles.

The rational behind this study was to evaluate mathematically the similarity in dissolution profile of two marketed aceclofenac tablet formulations using weighing approaches to consider batch to batch and within sample variability.

2. Investigations, results and discussion

The dissolution studies on two marketed aceclofenac tablets was performed in two media, acetate buffer pH 4.5

Table 1: Calculation of similarity by the conventional method

Reference (R)				Test (T)		
Phosphate buffer pH 6.8				Phosphate buffer pH 6.8		
Time (min)	Mean	SD	%CDR	Mean	SD	%CDR
15	0.434833	0.012883	49.95	0.454917	0.039782	52.28
30	0.6385	0.015466	74.496	0.606351	0.03356	69.835
45	0.6735	0.015024	77.622	0.710167	0.034886	81.908
60	0.868833	0.040422	100.024	0.798	0.117524	92.157
Acetate buffer pH 4.5				Acetate buffer pH 4.5		
Time (min)	Mean	SD	%CDR	Mean	SD	%CDR
15	0.4465	0.034347	19.116	0.4475	0.024759	19.161
30	0.6695	0.023071	27.72	0.6545	0.020822	27.144
45	0.745167	0.017476	30.664	0.715333	0.015692	29.511
60	0.86575	0.042832	35.32	0.814	0.044725	33.377

$f_2 = 63.88$ (by conventional method), acetate buffer pH 4.5
$f_2 = 90.6804$ (by conventional method), phosphate buffer pH 6.8
The unit of time is minute, Mean represents mean of 12 observations, SD is standard deviation. f_2 was calculated using mean values, weight was equal to one

and phosphate buffer pH 6.8. The data were statistically analyzed by a model independent method using the three approaches. In the first step, the similarity factor was calculated using a conventional technique by taking weight as one ($w = 1$). The reported values of dissolution data for reference and test formulations and the calculated values of f_2 are depicted in Table 1.

2.1. Calculation of f_2 value using approach 1

The lower acceptable value of f_2 (i.e., 50) corresponds to 10% average absolute difference between a reference product and a test product at each time point. In reality, a dissolution study will show different values of difference between R and T at each time point, this variability will be referred to as within-sample variability; weight equal to one was given if the absolute difference between a reference and a test product is 10.

In this approach, at each time point, the optional weight (w) was calculated by taking the ratio of 50 to f_2^{Th}, where 50 is selected as the borderline value of similarity or dissimilarity of the batch as per acceptance criteria of the similarity factor (f_2), and f_2^{Th} is the conversion factor that takes into account variability between samples at each time point. The theoretical value of f_2^{Th} at each time point was calculated using the seminal equation suggested by Moore and Flanner. The conversion factor (f_2^{Th}) was calculated by the following equation:

$$f_2^{Th} = 50 \times \log\{[1 + (R - T)^2]^{-0.5} \times 100\} \qquad (2)$$

Similarly weight was calculated for a difference between reference and test formulations. For the calculation of modified similarity factor (f_2 – m1), values of mean dissolution data of a reference batch and test batches were used. The results are summarized in Table 2.

Table 2 displays the value of the similarity factor calculated by the conventional method (f_2) and by approach 1 (f_2 – m1), the proposed approach may ensure more meaningful comparison of the dissolution profiles than the conventional method since it encompasses the difference between R and T at each time point in dissolution testing.

2.2. Calculation of f_2 value using approach 2

To consider variability between samples, the optional weight (w) was calculated by taking the ratio of the absolute difference of mean percentage drug dissolved between R and T to 10% of percentage of drug dissolved from the reference formulation at each time point. The calculation for weight by this approach is shown in Table 3. Weight less than one was assigned to values lower than 10% of percentage of drug dissolved from reference at each time point. The obtained values of modified similarity factor (f_2 – m2) for the proposed and the classical method are shown in Table 3. The results of the test formulations revealed improved similarity in the dissolution profiles and lesser between sample variability, as f_2 value was higher than f_2 value calculated by approach 1.

Table 2: Calculation of similarity factor (f_2 – m1) by approach 1

Phosphate buffer pH 6.8				Acetate buffer pH 4.5			
Rt – Tt	f_2^{Th}	$W = 50/f_2^{Th}$	$W \times (Rt - Tt)2$	Rt – Tt	f_2^{Th}	$W = 50/f_2^{Th}$	$W \times (Rt - Tt)2$
2.33	79.801	0.6265	3.4015	0.045	99.97	0.5	0.00101
4.661	66.092	0.7565	16.43	0.576	96.889	0.516	0.17121
4.286	67.827	0.7371	13.541	1.153	90.822	0.5505	0.7316
7.867	55.03	0.9085	56.223	1.943	83.027	0.6022	2.2733
f_2 – m1 = 65.771				f_2 – m1 = 93.66			

$w = 50/f_2Th$ where, f_2Th: Conversion factor
f_2 – m1: Similarity factor calculated using approach 1

Table 3: Calculation of similarity factor (f_2 – m2) by approach 2

Phosphate buffer pH 6.8				Acetate buffer pH 4.5			
Rt – Tt	$(Rt - Tt)^2$	W	$W \times (Rt - Tt)^2$	Rt – Tt	$(Rt - Tt)^2$	W	$W \times (Rt - Tt)^2$
2.33	5.4289	0.4664	2.5320	0.045	0.002025	0.02354	0.00004
4.661	21.72	0.625	13.575	0.576	0.33177	0.2077	0.0689
4.286	18.369	0.5521	10.141	1.153	1.329	0.376	0.4997
7.867	61.8896	0.7848	48.570	1.943	3.775	0.5501	2.0766
f_2 – m2 = 67.64				f_2 – m2 = 94.50			

w = R – T/10% of R
f_2 – m2: Similarity factor calculated using approach 2

Table 4: Calculation of similarity factor (f_2 – m3) by approach 3

Phosphate buffer pH 6.8				Acetate buffer pH 4.5			
$(Rt - Tt)^2$	SD	W = 1 + SD/10	$w \times (Rt - Tt)^2$	$(Rt - Tt)^2$	SD	W = 1 + SD/10	$w \times (Rt - Tt)^2$
0.00062	0.035054	0.1035	0.00006415	0.00091	0.02178	0.1021788	0.00009
0.00088	0.018699	0.10186	0.00009	0.00117	0.01705	0.1017058	0.00012
0.00174	0.025845	0.102585	0.0001784	0.00099	0.01899	0.101899	0.00010
0.00872	0.111151	0.111115	0.0009696	0.00399	0.05584	0.1055849	0.00042
f_2 – m3 = 100				f_2 – m3 = 100			

w = (1 + SD/maximum allowed SD) = (1 + 0.0350/10) = 0.1035
f_2 – m3: Similarity factor calculated using approach 3

2.3. Calculation of f_2 value using approach 3

Approach 3 is an alternative method to calculate similarity factors using individual values of dissolution results of reference and test formulations in place of average dissolution data of a reference and a test product. In this approach, absolute difference between reference and test formulations at each sampling time in the dissolution test was used. 144 values of absolute difference between reference product (12 units) and test product (12 units) at the four sampling time points (15, 30, 45, 60 min) and Standard deviation (SD) of absolute difference between R and Tat each sampling time point were used in the calculation. The twelve units of test formulation will show different dissolution profiles and this variability is referred to as between samples variability in this study.

If the analyst-related variability and equipment-related variability is assumed as negligible, variability in dissolution data is not anticipated from reference or test formulation. Under these circumstances, the SD of absolute difference between R and T shall be zero. Weight equal to one was used when standard deviation is equal to zero. It is proposed that the value of weight should proportionally increase as SD increases. In this approach, the weight was calculated from the equation (1 + SD/maximum allowed SD). The maximum allowed SD was arbitrarily chosen as 10 to allow within samples as well as variability between samples. The weights, standard deviations and the values of similarity factor (f_2 – m3) are shown in Table 4.

The results revealed that the similarity factor was calculated on not just the average data but on each and every dissolution data and it was found to be 100 for both the media which indicated that the dissolution profiles of the two marketed formulations were most similar.

Approach 3 must be given maximum preference, as it considers batch-to-batch as well as within-samples variability and shows the best similarity profile. Approach 2 is given more preference over approach 1 because it considers batch-to batch variability with more specificity as compared to approach 1. On the basis of consideration of variability, the three approaches are given preference in the order of approach 3 > approach 2 > approach 1 (Table 5).

3. Experimental

3.1. Materials

Aceclofenac was gifted by Mepro pharmaceutical pvt.ltd, Surendranagar. Potassium dihydrogen orthophosphate, sodium dihydrogen orthophosphate, were obtained from Qualigens, sodium hydroxide and sodium acetate were obtained from S.D.Fine chemicals, Mumbai, methanol (AR grade), hydrochloric acid (Merck, Darmstadt, Germany), were used. Double distilled water was used throughout the study. Aceclofenac tablet formulations (100 mg) were procured commercially.

3.2. Dissolution studies

The two commercial tablet formulations of aceclofenac (100 mg) were procured from the local market and subjected to dissolution study. Dissolution study was carried out using USP dissolution apparatus II at a paddle speed of 50 rpm at 37 ± 0.5 °C in 900 ml dissolution media (acetate buffer pH 4.5 and phosphate buffer pH 6.8) for 12 tablets of each formulation. Samples (5 ml) were withdrawn every 15 min up to 1 h. Samples were replaced with fresh medium each time. Drug release was analyzed spectrophotometrically at 275 nm.

3.3. Statistical analysis

The data obtained from the dissolution study were subjected to statistical analysis using model independent method. Various weighing approaches were used for calculation of similarity factor (f_2).

Table 5: Comparison of similarity factor with conventional method and proposed approaches

Dissolution media	Conventional method	Approach 1	Approach 2	Approach 3
Acetate buffer pH 4.5	90.68	93.66	94.50	100
Phosphate buffer pH 6.8	63.88	65.77	67.64	100

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