CHAPTER 10

MATHEMATICAL APPROACH FOR THE

ASSESSMENT OF SIMILARITY FACTOR USING A

NEW SCHEME FOR CALCULATING WEIGHT

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10. New Scheme for Calculating Weight

10.1 Introduction

Moore and Flanner proposed two new indices ($f_1$ and $f_2$) to compare dissolution profiles of a test and a reference formulations (Moore, 1996). The concept of similarity factor ($f_2$) has been endorsed by FDA; therefore, it is widely adopted in formulation and development and dossier preparation. Recently, Gohel and co-workers suggested three different schemes for calculating weight to compute similarity factor (Gohel, 2005). In the present work, an additional scheme for calculating weight is proposed and its impact on value of similarity factor is compared.

The equation proposed by Moore and Flanner is given below (Moore, 1996).

$$f_2 = 50 \times \log\left\{1 + \frac{1}{n} \sum_{i=1}^{n} w_i (R_i - T_i)^2 \right\}^{-0.5} \times 100$$

Where, $f_2$ is similarity factor, $n$ is the number of observations, $w_i$ is optional weight, $R_i$ is average percentage drug dissolved from reference formulation, and $T_i$ is average percentage drug dissolved from test formulation. Generally, average of twelve observations is used for calculating $f_2$. Optional weight factor ($w_i$) is usually considered as unity.

It is stated in the guidance document that the percent coefficient of variation (% CV) should not be more than 20% at the earlier time points, and it should not be more than 10% at other time points when mean dat is to be used for calculation of indices (USFDA, 1997). These values are considered as maximum allowable %CV in the present work. One of the objectives of the proposed work was to incorporate these conditions in calculation of $f_2$. 
10.2 The New Scheme for Calculating Weight

The new scheme for calculating weight shows impact of within sample variability on $f_2$ value. Weight ($w_t$) is calculated using equation 2.

$$w_t = 1 + \frac{\% CV \ of \ R_t}{MCV_{E/L}} + \frac{\% CV \ of \ T_t}{MCV_{E/L}} \quad \ldots (2)$$

Where, $w_t$ is weight, $\% CV$ of $R_t$ and $\% CV$ of $T_t$ are the percentage coefficient of variation of reference and test products respectively. $MCV_{E/L}$ is the maximum allowable $\% CV$. $MCV_{E/L}$ was 20 for earlier time point (30 min) and it was 10 for later time points (above 30 min). Co-efficient of variation was calculated using the following equation 3.

$$\% CV = \frac{SD}{Mean} \times 100 \quad \ldots (3)$$

If the $\% CV$ of $R_t$ and $\% CV$ of $T_t$ is equal to zero, $w_t$ is equal to one.

10.3 Determination of Similarity Factor for Formulated Dosage Forms.

Three formulations (A, B and C) were prepared. Formulation A was capsule containing two floating tablet of rifampicin plus one enteric coated isoniazid capsule. Formulation B was a capsule containing floating minimatrices of rifampicin plus enteric minitablets of isoniazid. Formulation C was made up of gastro-retentive minitablets of rifampicin plus enteric sustained release microcapsules of isoniazid. The in vitro drug release profile of these formulations was utilized for calculating similarity factor. The in vitro drug release study was carried out by the method mentioned in chapter 5. Table 10.1 shows in vitro drug release profile of formulations A, B and C.
Table 10.1: In vitro drug release profile of formulations A, B and C.

| Time in hr | A       | B       | C       |
|------------|---------|---------|---------|
|            | *Average | SD      | *Average | SD      | *Average | SD      |
| 1          | 20       | 1.9     | 21       | 2.2     | 18       | 1.1     |
| 2          | 44       | 3.3     | 40       | 3.1     | 42       | 1.5     |
| 3          | 78       | 4.1     | 82       | 3.2     | 79       | 3       |
| 4          | 98       | 2.6     | 95       | 1.6     | 97       | 2       |

n = 12, SD = Standard Deviation, Average = Average of percentage drug release at that time point.

* Average of rifampicin determined (undegraded) for 12 different units at that time point.

10.4 Results and discussion

Gohel and co-workers stated that the approach 3 was the best amongst other approaches for calculating weight (Gohel, 2005). In approach 3, reference product (12 units) and test product (12 units) were used to generate 144 values of absolute difference between a reference and a test formulation at the four sampling time points (30, 60, 90 and 180 min). Standard deviation (SD) of the 144 values was calculated. The twelve units of test formulation will show different dissolution profiles and this variability is referred to as between samples variability. The weight was calculated from the equation (1 + SD/maximum allowable SD). The maximum allowable SD was arbitrarily chosen as 10. It was arbitrarily decided to give weight equal to one when standard deviation is equal to zero.

The value of similarity factor (f2) is 100 when the difference between reference and test formulation is zero and weight (w1) is unity. Gohel and co-workers further reported that
as the value of weight \((w_i)\) increases, a decrease in the value of similarity factor is anticipated (Gohel, 2005).

Table 10.2: Dissolution data for calculating \(f_2\) values

| Reference | Test 1 | Test 2 |
|-----------|--------|--------|
| Time      | Average | SD     | Time | Average | SD | Time | Average | SD |
| 30        | 34.92   | 2.26   | 30   | 40.34   | 4.1 | 30   | 49.33   | 2.32 |
| 60        | 59.5    | 3.85   | 60   | 67.15   | 6.34| 60   | 65.33   | 5.02 |
| 90        | 79.27   | 5.12   | 90   | 87.01   | 4.76| 90   | 86.75   | 3.52 |
| 180       | 95.08   | 6.14   | 180  | 97.73   | 1.48| 180  | 102.83  | 1.72 |

\(f_2 = 60.04\) \(f_2 = 51.08\)

| Test 3 | Test 4 | Test 5 |
|--------|--------|--------|
| Time   | Average | SD     | Time | Average | SD | Time | Average | SD |
| 30     | 25.8    | 2.36   | 30   | 15.08   | 5.78| 30   | 43.39   | 1.29 |
| 60     | 50.64   | 4.64   | 60   | 59.5    | 3.07| 60   | 77.96   | 1.43 |
| 90     | 67      | 6.14   | 90   | 79.27   | 4.32| 90   | 86.33   | 2.8 |
| 180    | 88.6    | 8.12   | 180  | 95.08   | 2.68| 180  | 95.58   | 1.99 |

\(f_2 = 51.19\) \(f_2 = 50.07\) \(f_2 = 48.05\)

The unit of time is minute, Average is average of 12 observations, SD is standard deviation. (Shah, 1998)

To demonstrate the utility of the new approach to calculate weight, the dissolution data reported by Shah et al., were used (Shah, 1998). The average value of cumulative percentage drug dissolved for reference (R) and test (T) formulations are shown in Table 10.2. The standard deviation and average of dissolution data of reference and test formulations were calculated at each sampling time. The results are shown in Table 10.3.

Table 10.4 displays the value of similarity factor calculated using the new approach \((f_2-m)\) and approach 3 \((f_2-m_3)\) of our earlier publication. The results shows that the value of...
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\( f_{2-m} \) was lower than the value of \( f_{2-m3} \) in all the cases (test 1 to test 5). The new approach appears to be more sensitive than the approach 3 proposed in the earlier publication since within sample variability is incorporated in the new approach.

### Table 10.3: Sample calculation for weight \((w_i)\) for test formulation 1.

| Time | R   | T   | SDR | SDT | CVR | CVT | \(w_i\) |
|------|-----|-----|-----|-----|-----|-----|---------|
| 30   | 34.92 | 40.34 | 2.26 | 4.10 | 6.47 | 10.16 | 1.83    |
| 60   | 59.50 | 67.15 | 3.85 | 6.34 | 6.47 | 9.44  | 2.59    |
| 90   | 79.27 | 87.01 | 5.12 | 4.76 | 6.45 | 5.47  | 2.19    |
| 180  | 95.08 | 97.73 | 6.14 | 1.48 | 6.45 | 1.51  | 1.79    |

\( R = \text{Reference}, T = \text{Test 1}, SDR = \text{Standard deviation of} \ R, SDT = \text{Standard deviation of} \ T, CVR = \% \text{CV of} \ R, CVT = \% \text{CV of} \ T, w_i = 1 + (\% \text{CV of} \ R/\text{MCVe}) + (\% \text{CV of} \ T/\text{MCVe}) \)

### Table 10.4: Similarity factors for different test formulations

| Test formulations | \( f_{2-m} \) | \( f_{2-m3} \) | \( f_2 \) |
|-------------------|--------------|--------------|---------|
| 1                 | 51.34        | 54.68        | 60.04   |
| 2                 | 45.01        | 46.88        | 51.08   |
| 3                 | 41.86        | 48.30        | 51.19   |
| 4                 | 37.38        | 46.46        | 50.07   |
| 5                 | 42.05        | 44.98        | 48.05   |

\( f_{2-m} = \text{Similarity factor calculated using new approach}, f_{2-m3} = \text{Similarity factor calculated using approach 3}, f_2 = \text{Similarity factor calculated using conventional method} \)

Table 10.4 displays the value of similarity factor calculated using the new approach \( (f_{2-m}) \) and approach 3 \( (f_{2-m3}) \) of our earlier publication. The results shows that the value of \( f_{2-m} \) was lower than the value of \( f_{2-m3} \) in all the cases (test 1 to test 5). The new approach appears to be more sensitive than the approach 3 proposed by Gohel and co-
In the new scheme of weight \( w_i \) calculation, no parameter was decided on an arbitrary ground. The new approach appears to be more realistic as compared to approach 3. Another advantage of the new method is simple calculation steps than approach 3. Equal stress is given to variability in reference and test formulation in the new approach. The maximum allowable \%CV, as proposed in FDA guidance document, is also considered in the proposed method. It considers within samples (12 units of reference and 12 units of test) as well as between samples (reference and test formulations) variability because of utilization of SD and averages of reference and test formulations at each time point for calculating weight.

**Table 10.5: The similarity factor of formulations A, B, and C.**

| Similarity factor | AB    | BC    | AC    |
|-------------------|-------|-------|-------|
| \( f_2 \)        | 73.48 | 78.12 | 86.4  |
| \( f_{2m} \)     | 66.2  | 72.5  | 81.04 |

\( f_{2.m} = \text{Similarity factor calculated using new approach, } f_2 = \text{Similarity factor calculated using conventional method (} w_i = 1). \)

AB = value of comparison of formulation A and B.
BC = Value of comparison of formulation B and C.
AC = Value of comparison of formulation A and C.

Table 10.5 shows that the values of similarity factors falls between 50-100 in both the cases. Hence, the in vitro drug release profile of all the formulations A, B and C can be
considered as similar. The similarity factor of formulations A, B and C decreased significantly the new scheme of calculating weight was adopted.

10.5 Conclusion
The use of new method is recommended in deciding equivalence of test product with innovators product. The approach may also find application in selection of a bio-batch. The use of new approach may become a strong point in ANDA submission. If all the three yields $f_2$ greater than 50 than we may safely assume that products show similar dissolution. The positive and negative points of the new approach will emerge out when various researchers will try the approach with their data sets.

10.6 References
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