Nomogram for Computing the Value of Similarity Factor

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Gohel, *et al.:* Similarity Factor Nomogram

The objective of present work was to construct nomogram for obtaining a value of similarity factor (f_2) by employing the values of number of observations (n) and sum of squared difference of percentage drug dissolved between reference (R) and test (T) products $\left(\sum_{i=1}^{n}(R_i - T_i)^2\right)$. The steps for rearrangement of equation of similarity factor are presented.

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The values of f_2 were selected in the range of 45 to 100 for 4 to 12 observations (n) for computing the values of $\sum_{i=1}^{n}(R_i - T_i)^2$. Linear regression analysis was performed between number of observations and $\left(\sum_{i=1}^{n}(R_i - T_i)^2\right)$. Perfect correlation was observed in each case. Nomogram was constructed and later it was validated by using drug dissolution data from literature and our laboratory. The use of nomogram is recommended during research and development work to investigate effect of formulation or process variables. The nomogram can also be used during change in manufacturing site or change in equipment. It is concluded that the steps for calculation of f_2 can be truncated in the middle (i.e. at the step of calculation of factor $\left(\sum_{i=1}^{n}(R_i - T_i)^2\right)$ and a decision of similarity/dissimilarity can be taken employing the nomogram.

Key words: Dissolution, nomogram, rearranged similarity function equation, similarity factor

The dissolution test is the most powerful performance test for solid oral dosage forms. Dissolution test is mainly used in the pharmaceutical industry for the measurement of batch-to-batch variability, i.e. for quality control purposes. The selected classical uses of the dissolution test include formulation and development work, selection of bio-batch, surrogate for *in vivo* test and establishment of *in vivo in vitro* correlation (IVIVC). The batch for bioequivalence study (biobatch) is selected considering the similarity of dissolution from reference and test products in multiple biorelevant dissolution media. The data for dissolution study and bioequivalence are generally demanded by FDA in ANDA applications.

A nomogram, a two-dimensional graph, is constructed to permit the approximate computation of a mathematical function. Most nomograms are used in applications where an approximate answer is appropriate and useful. Nomogram may also be used to check an answer obtained from an exact calculation method, i.e. for validation. In the present study, a nomogram is constructed for obtaining a value of similarity factor (f_2).

Generic version of drug formulations has become popular due to cost benefit to the patients. During the development of generic formulation, similarity of dissolution between reference and test formulations is checked in multiple dissolution media. Moore and Flanner presented a model independent approach for expressing similarity and dissimilarity between dissolution profiles[1]. The equation of similarity factor is widely used in the pharmaceutical industry after its endorsement by USFDA[2]. The SUPAC-IR guideline also indicate that the dissolution profile can be compared using the similarity factor[3].

FDA guideline mentions that twelve units each of test and reference products must be employed for computing similarity factor using the mean dissolution values at each sampling time. To allow use of mean data, the percent coefficient of variation at the earlier time points (e.g. 15 min) should not be more than 20% and at other time points should not be more than 10%.

The dissolution measurements of the test and reference batches should be made under the same conditions. The dissolution time points for both the profiles should be the same. It is common practice to use relatively dense and equally spaced sampling time[4]. Only one measurement should be considered after 85% drug dissolution of both the products. The reference batch should be the most recently manufactured product.

As per EMEA guidelines, the evaluation of similarity is based on; (1) a minimum of three time points (zero excluded); (2) twelve individual values for every time points for each formulation; (3) not more than one mean value of greater than 85% drug dissolved for each formulation; (4) the standard deviation of the mean of any product should be less than 10% from second to last time points, and (5) in cases where more than 85% of the drugs are dissolved within 15 min, dissolution profiles may be accepted as similar without further mathematical evaluation[5].

Similarity factor can be used for dissolution profile comparison of formulations on switching over from one equipment to equipment. The impact of process variables can be examined by comparing dissolution profiles. The concept of quality by design is preferred by USFDA. The most integral parts of QbD are design of experiment (DOE) and design space. Singh and co-workers mentioned that DOE represent effective and cost-effective analytical tools to yield the optimal solution to a particular problem[6]. Singh

and co-workers remarked that formulation by design is a holistic concept of formulation development aiming to design more efficacious, safe, economical and patient-compliant drug delivery system[7]. Flanner and co-workers used similarity and dissimilarity factors as dependent variables in D-optimal design[8].

In design of experiment (DOE), f_2 or $\sum_{i=1}^{n}(R_i - T_i)^2$ can be selected as a response (dependent variable). The objective of undertaking present study was to simplify the calculation of similarity factor by terminating the calculations at an intermediate step. The Eqn. for similarity is as follows: $f_2 = 50\log\left\{\left[1+\frac{1}{n}\sum_{i=1}^{n} w_i(R_i - T_i)^2\right]^{-\frac{1}{2}} \times 100\right\}$ ... (1), where f_2 is similarity factor, n is number of observations, w_i is an optional weight factor and R_i and T_i represents the percentage drug dissolved from reference and test formulations respectively at different time points.

In the present study percent drug dissolved at all sampling time points were treated as equally important and therefore equal weight was given to data set at each sampling time point (w_i=1). The steps for rearrangement of the similarity factor are shown below:

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

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

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

$$10^{(f_2/50)} = \left\{\left[1+\frac{1}{n}\sum_{i=1}^{n}\left(R_i - T_i\right)^2\right]^{-\frac{1}{2}} \times 100\right.$$

$$\frac{10^{(f_2/50)}}{100} = \left[1+\frac{1}{n}\sum_{i=1}^{n}\left(R_i - T_i\right)^2\right]^{-\frac{1}{2}}$$

$$\left\{\frac{10^{(f_2/50)}}{100}\right\}^{-2} = 1+\frac{1}{n}\sum_{i=1}^{n}\left(R_i - T_i\right)^2$$

$$\left\{\frac{10^{(f_2/50)}}{100}\right\}^{-2} - 1 = \frac{1}{n}\sum_{i=1}^{n}\left(R_i - T_i\right)^2$$

$$n \times \left[\left\{\frac{10^{(f_2/50)}}{100}\right\}^{-2} - 1\right] = \sum_{i=1}^{n}\left(R_i - T_i\right)^2 \quad (2)$$

For the construction of nomogram, the values of similarity factor (f_2) were chosen in the range of 45 to 100 with a step size of five and the number of observations (n) was selected in the range of 4 to 12 with a step size of one in eqn. 2. The computed values of sum of squared difference between reference and test products for selective f_2 values are shown in Table 1.

Researchers can use the grid shown in Table 1 for computation of similarity factor by employing the values of $\sum_{i=1}^{n}(R_i - T_i)^2$ (D) and n. A diagrammatic representation of data is always easier to interpret and therefore an effort was made to generate nomogram by performing linear regression analysis between the number of observations and the sum of squared difference of percentage drug dissolved between reference and test products for the selected values of similarity factor (45 to 99.99). Figs. 1 and 2 show the nomogram. Two figures were drawn in place of one figure to improve readability of data. The value of correlation coefficient was unity in all the cases, indicating a perfect fit between the independent variable (n) and dependent variable $\left(\sum_{i=1}^{n}(R_i - T_i)^2\right)$.

For validation of the concept, data of dissolution studies were picked up from literature[9-13]. The similarity factor, computed using Eqn. 1, was compared with that obtained from the nomogram in

TABLE 1: COMPUTED VALUES OF SUM OF SQUARED DIFFERENCE BETWEEN REFERENCE AND TEST PRODUCTS (EQN. 2)

n	f_2	*D*	n	f_2	*D*	n	f_2	*D*	n	f_2	*D*
4	50	396	4	65	96.48	4	83	15.15	4	99.99	0.0037
5		495	5		120.59	5		18.93	5		0.0046
6		594	6		144.71	6		22.72	6		0.0055
7		693	7		168.83	7		26.50	7		0.0065
8		792	8		192.95	8		30.29	8		0.0074
9		891	9		217.07	9		34.08	9		0.0083
10		990	10		241.19	10		37.86	10		0.0092
11		1089	11		265.31	11		41.65	11		0.0101
12		1188	12		289.43	12		45.44	12		0.0110

n: Number of observations, f_2: Similarity factor and D: $\left(\sum_{i=1}^{n}(R_i - T_i)^2\right)$

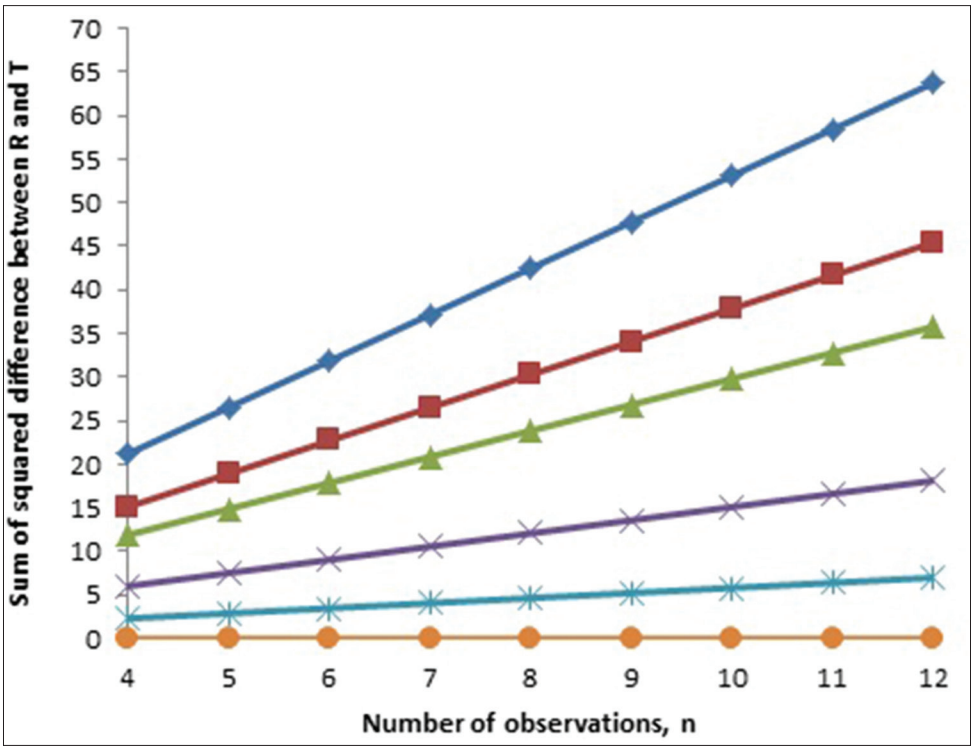

Fig. 1: Nomogram for computation of similarity factor (f2 = 80 to 99.9).
The similarity factor can be obtained by intersecting the X axis (number of observations) and Y axis (sum of squared difference between R and T). F2=80, F2=83, F2=85, F2=90, F2=95, F2=99.9.

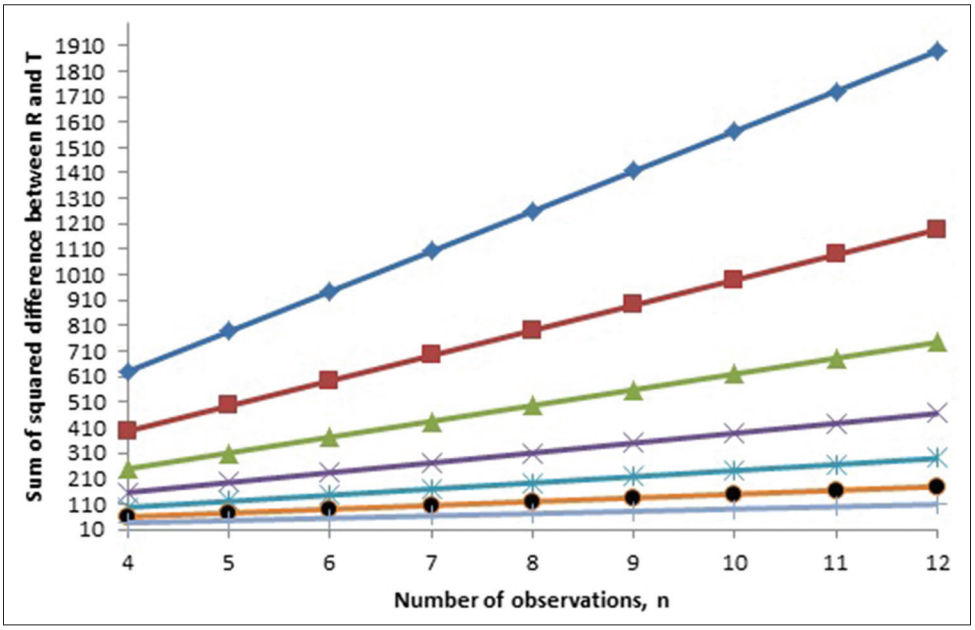

Fig. 2: Nomogram for computation of similarity factor (f2 = 45 to 75).
The similarity factor can be obtained by intersecting the X axis (number of observations) and Y axis (sum of squared difference between R and T). F2=45, F2=50, F2=55, F2=60, F2=65, F2=70, F2=75.

each case and it was confirmed that the nomogram can be used by scientist for calculation of similarity factor and for drawing conclusion of similarity/ dissimilarity between two dissolution curves. The results are depicted in Table 2.

Quetiapine fumarate extended release tablets (test product) were developed in our laboratory. Seroquel XR was chosen as a reference product. Dissolution study was conducted in 0.1 N HCl for 2 h followed by 6.2 pH phosphate buffer for up to 20 h, USP

type I apparatus, 100 rpm for the test and the reference product. The samples were collected at 2, 4, 6, 8, 12, 16, and 20 h (n=7). The average percent drug dissolution from the test and reference product were 34 (35), 49 (45), 57 (55), 65 (66), 77 (80), 90 (92), and 99 (100). The data in parenthesis represneted for the reference product (Seroquel XR). The value of sum of squared difference between the reference and the test product was 36 and similarity factor (f_2) was calculated as 80.29 using the equation suggested by Moore and Flanner[1]. Nomogram shown in fig. 1 yielded a value of 80.

TABLE 2: RESULTS FOR LITERATURE DATA SETS FOR VALIDATION

n	$\left(\sum_{i=1}^{n}(R_i-T_i)^2\right)$	f_2	Reference Number
4	154.83	60.02	6
4	357.645	51.09	6
4	354.22	51.19	6
4	393.63	50.06	6
4	474.61	48.06	6
8	1719.26	41.64	7
7	193.202	63.58	8
12	712.09	55.48	9
7	57.792	75.83	10
7	4472.8	29.84	10

$\left(\sum_{i=1}^{n}(R_i-T_i)^2\right)$ and f2 were calculated using actual data, and Eqn. 1 respectively

The dissolution profiles are dissimilar (f_2<50) if the computed values of sum of squared difference between reference and test products $\left(\sum_{i=1}^{n}(R_i-T_i)^2\right)$ are higher than 396, 495, 594, 693, 792, 891, 990, 1089 and 1188 for numbers of sampling times 4, 5, 6, 7, 8, 9, 10, 11 and 12 respectively (See Table 1). The reverse is true (f_2>50) if the computed values of $\left(\sum_{i=1}^{n}(R_i-T_i)^2\right)$ are lower than the values stated above.

For the computation of similarity factor, USFDA recommends use of twelve observations[2]. The data shown in Table 3 were evolved using eqn. 2. Table 3 can be used for precise computation of similarity factor if the factor $\sum_{i=1}^{n}(R_i-T_i)^2$ is known for n equal to 12. Similar tables can be constructed for different number of observations (n) using Eqn. 2.

Shah *et al*. reported that if the computed value of f_2 is 50, 65 or 83, the dissolution profiles can be considered as similar at 10, 5 and 2 % difference between reference and test products respectively [9]. If the computed value of $\sum_{i=1}^{n}(R_i-T_i)^2$ is in between the contour lines of f_2 equal to 50 and 65, it is concluded that the dissolution profiles are similar at 5 to 10% difference between reference and test products. However, if the computed value of $\sum_{i=1}^{n}(R_i-T_i)^2$ is in between the lines of f_2 equal to 65 and 83, the dissolution profiles are similar at 2 to 5 % difference

TABLE 3: SIMILARITY FACTOR FOR TWELVE OBSERVATIONS

$\sum_{i=1}^{n}(R_i-T_i)^2$	f_2	$\sum_{i=1}^{n}(R_i-T_i)^2$	f_2	$\sum_{i=1}^{n}(R_i-T_i)^2$	f_2	$\sum_{i=1}^{n}(R_i-T_i)^2$	f_2	$\sum_{i=1}^{n}(R_i-T_i)^2$	f_2
109429	1	17333	21	2737.0	41	423.69	61	57.05	81
99800	2	15807	22	2495.2	42	385.36	62	50.98	82
91017	3	14415	23	2274.6	43	350.39	63	45.44	83
83008	4	13146	24	2073.4	44	318.51	64	40.38	84
75703	5	11988	25	1889.9	45	289.43	65	35.77	85
69041	6	10932	26	1722.5	46	262.90	66	31.57	86
62965	7	9969	27	1569.9	47	238.72	67	27.74	87
57424	8	9091	28	1430.7	48	216.66	68	24.24	88
52370	9	8290	29	1303.8	49	196.54	69	21.05	89
47761	10	7559	30	1188.0	50	178.19	70	18.14	90
43557	11	6893	31	1082.4	51	161.45	71	15.49	91
39724	12	6286	32	986.1	52	146.19	72	13.07	92
36227	13	5732	33	898.3	53	132.27	73	10.87	93
33039	14	5226	34	818.2	54	119.58	74	8.85	94
30131	15	4765	35	745.1	55	108.00	75	7.02	95
27478	16	4345	36	678.5	56	97.44	76	5.35	96
25060	17	3962	37	617.8	57	87.81	77	3.82	97
22854	18	3612	38	562.4	58	79.03	78	2.43	98
20842	19	3293	39	511.8	59	71.02	79	1.16	99
19007	20	3002	40	465.7	60	63.71	80	0.00	100

f_2: Similarity factor

between reference and test products. If the computed value is below the line of f_2 equal to 83, the dissolution profiles are considered similar at 0 to 2 % difference between reference and test products. Radar diagram is presented in fig. 3 to display the results graphically for f_2 equal to 50 and 65. If the computed value of $\sum_{i=1}^{n}(R_i - T_i)^2$ is within the inner enclosed geometrical area, the curves are similar at ≤5% level and the outer enclosed area indicate similarity at ≤10%. The dissimilar region is appropriately defined in the radar diagram.

The concept presented in the present work can find endless industrial applications demanding comparison of dissolution profiles. The concept of quality by design (QbD) and use of Design of Experiment (DOE) have become popular in recent time. The factor $\sum_{i=1}^{n}(R_i - T_i)^2$ can be used as a dependent variable in DOE. Normal operating range (NOR) can be used in the contour plot depicting the effect of two independent variables IV's on the factor $\sum_{i=1}^{n}(R_i - T_i)^2$.

Moore and Flanner expressed curvilinear relationship between similarity factor (f_2) and average difference between percentage drug dissolved from reference and test curves[1]. Model fitting was done employing the values of log $\sum_{i=1}^{n}(R_i - T_i)^2$ (y-axis) and f_2 (x-axis). A reasonable linearization (correlation coefficient=0.989) was achieved on using semi logarithmic plot for each observation (n=4 to 12). The values of slope and intercept can also be used for arbitrary calculation of similarity factor. If grid search technique is adopted with this approach, exact computation of f_2 is not feasible as the value of correlation coefficient is less than one.

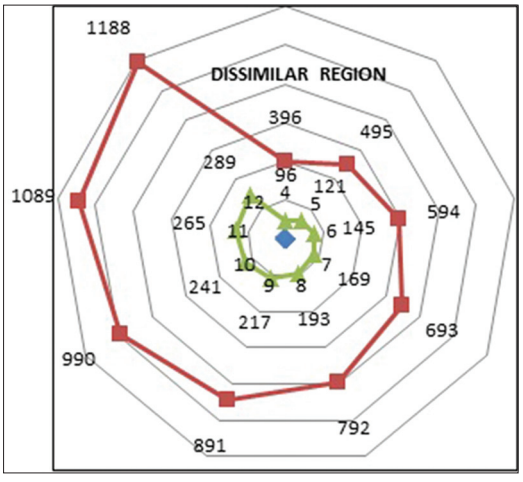

Fig. 3: Radar diagram for similarity factor equal to 50 and 65. As the number of sampling time increases, the sum of squared difference between R and T increases. n, F2=50, F2=65.

Two nomograms are presented in the present study for computation of similarity factor. The data for the construction of nomogram are presented in a grid form. The nomogram was successfully used to compute value of similarity factor for the data reported in literature. A lot of men hours can be saved in pharmaceutical industry if the expanded grid is prepared, once only, containing calculations for f_2 from 0 to 100 with a step size of one unit. Moreover, the expanded grid can be used for the validation purpose for the calculations of similarity factor by regulators. The use of nomogram is recommended for novice as well as for the scientists who are running in short of time since the calculation steps for obtaining the value of f_2 are truncated. The terminal steps for calculation of f_2 (logarithm and square root functions) are eliminated, which necessitates the need of computers, time, accuracy in calculation and trained personnel. The simplified approach, proposed in present work, is user friendly.

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