Original Article

Application of Similarity Factor (f_2) and Time Required to Drug Release ($t_{\%}$) Indicators for Dissolution Profiles Comparison of Paracetamol Tablets

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ABSTRACT

Introduction: The comparison of *in vitro* dissolution profiles is an integral step during the development of any generic product. However, using merely similarity factor (f_2) as a dissolution parameter may not be adequate. **Objectives:** The present study was conducted to explore whether f_2 alone suffices to adequately compare the dissolution profiles of tablets or both f_2 and time required to percentage drug release ($t_{\%}$) generate closely similar results. **Methods:** The reference (R) and two generic paracetamol test products (T1 and T2), each containing 500 mg drug were subjected to dissolution studies under different pH conditions namely 1.2, 4.5 and 6.8. The amount of drug released was quantified using validated UV-Visible spectrophotometric method and results were analysed using bootstrap similarity factor approach and the time required to release 25% ($t_{25\%}$), 50% ($t_{50\%}$) and 75% ($t_{75\%}$) of drug. The data were evaluated statistically using one-way multivariate analysis of variance (MANOVA) followed by post hoc Tukey's test. **Results:** T1 tablets demonstrated similarity in the drug release with R product at pH 1.2. Although T2 product did not show any similarity with R at all pH values used yet it depicted rapid release profiles pivotal for an immediate-release product. Both f_2 and $t_{\%}$ exhibited closely similar results for all sets of data. **Conclusion:** Application of similarity factor alone may provide reliable results for comparison of dissolution profile. Nevertheless, the time required to release $t_{25\%}$, $t_{50\%}$ and $t_{75\%}$ may be used along with similarity factor for better interpretation of *in vitro* dissolution results particularly for potent drugs.

Key words: Similarity factor, Time to drug release, Dissolution profiles, Paracetamol tablets, UV-Visible spectrophotometer, Statistical analysis.

INTRODUCTION

In vitro dissolution testing of solid oral dosage forms such as tablet, capsule or pellets serves as an essential tool in pharmaceutical industry to provide information concerning the quality of medicine in terms of batch-to-batch consistency (quality control) and to predict the *in vivo* drug release performance. The dissolution test measures drug release *in vitro* as a function of time under standardised sink conditions (e.g. dissolution medium, pH, agitation speed and temperature). The comparison of *in vitro* dissolution profile of a test product with that of a reference or an innovator product is a mandatory requirement during the development of a test or generic formulation.[1] The comparison of *in vitro* dissolution profiles can be carried out using several established methods or parameters such as exploratory data analysis methods, statistical methods, model dependent and model independent methods.[2,3] Among these, the model independent parameters namely similarity factor (*f2*) is attaining immense attention due to recommendations and legislations imposed by various regulatory authorities throughout

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the world.[2,4-7] According to U.S. Food and Drug Administration (USFDA), similarity factor is defined as the logarithmic reciprocal square root transformation of one plus sum of the squared differences between the dissolution values of test and reference products over all time points.[5] The f_2 value of more than 50 on a scale ranging between 0 and 100 indicates the close similarity between two *in vitro* dissolution profiles and could be considered as a rationale to conduct the *in vivo* bioequivalence study if required.

Although similarity factor is simple to calculate and only uses a single number to describe the difference between the *in vitro* dissolution profiles, its application has also received some criticisms primarily ascribable to its conceptual and statistical limitations.[8,9] For instance, firstly the basic criteria to declare similarity between the *in vitro* dissolution profiles (f_2 profile lacks the strong statistical justifications.[10,11] Secondly, statistical hypothesis cannot be formulated because it is impossible to evaluate the probability and rate of false positive or negative results.[12] Thirdly, the value of f_2 is sensitive to the number of time points selected for a particular dissolution profile and lastly, f_2 is insensitive to shape of dissolution curves as its results do not demonstrate the extent and degree of deviation between the *in vitro* dissolution profiles.[2,5,12]

Owing to the aforementioned limitations, application of similarity factor alone as a parameter to compare the *in vitro* dissolution profiles during the development of a generic tablet, capsule or pelletised product may not yield the accurate and reliable comparison of the *in vitro* dissolution profiles of innovator and generic products. Therefore, the present study was also conducted with an aim to employ another dissolution parameter namely time required to percentage drug release in terms of 25% ($t_{25\%}$), 50% ($t_{50\%}$) and 75% ($t_{75\%}$). The specific aim or research question of the study was to explore whether both similarity factor and time required to percentage drug release generate closely similar results or similarity factor alone suffices to adequately compare the dissolution profiles of tablets?

MATERIALS AND METHODS

Materials

The various materials and products employed in the present study were analytical grade paracetamol powder (Merck-Schuchardt, Germany), potassium chloride (Sigma-Aldrich, USA), 37% w/w hydrochloric acid (Fisher Scientific, UK), anhydrous sodium acetate (Fisher Scientific, UK), glacial acetic acid (Merck KGaA, Germany), potassium dihydrogen orthophosphate (Fisher Scientific, UK) and sodium hydroxide (Merck KGaA, Germany). The innovator paracetamol immediate-release tablets were used as a reference product (R) and two generic products marketed in Malaysia were used as test products (denoted as T1 and T2, respectively) for the comparison of *in vitro* dissolution profiles mathematically. All tablets products contained 500 mg paracetamol as an active ingredient.

Development and validation of UV/Visible-spectrophotometric analytical Method

Various parameters such as linearity, range, precision, accuracy, limit of quantitation and detection were assessed according to International Conference on Harmonization (ICH) guideline Q2 (R1): Text on Validation of Analytical Procedures and Methodology.[13] Published protocols were followed with slight modifications to prepare a calibration curve of paracetamol in a concentration range between 5.0 and 25.0 μg/mL using 0.1 M NaOH as a medium.[14,15] The absorbance values were measured in triplicate using UV/Visible-spectrophotometer at a wavelength (λ) of 255.6 nm. The method was validated in terms of linearity, range, precision and accuracy using three known concentrations of paracetamol solutions (5.0, 15.0 and 25.0 μg/mL).

In vitro dissolution study

The *in vitro* dissolution studies were performed using 900 mL of buffer solutions: 0.085 M hydrochloric acid (pH 1.2), acetate buffer (pH 4.5) and phosphate buffer (pH 6.8) using USP Dissolution Apparatus 1 (basket type) maintained at rotation speed of 50 rpm and temperature value of 37 ± 0.5°C. One tablet containing 500 mg of paracetamol was placed into each dissolution vessel followed by the withdrawal of 3 mL sample at predetermined time intervals of 5, 10, 15, 20, 30, 45, 60, 90 and 120 min. The withdrawn sample was replaced with the same amount of fresh dissolution medium to maintain the sink conditions. All collected samples were filtered, serially diluted and analysed using UV/Visible-spectrophotometer at 255.6 nm. Experiment was performed in six replicates. Statistical analysis of similarity factor was performed using DDSolver program[16,17] whereas $t_{25\%}$, $t_{50\%}$ and $t_{75\%}$ values were processed using one-way multivariate analysis of variance (ANOVA) followed by post hoc Tukey's test using SPSS software (IBM, Version 25, USA).

Quality evaluation of tablets

The quality evaluation of all tablet products in terms of various parameters such as friability, weight variation, content uniformity, hardness and thickness was

performed. Friability, weight variation and content uniformity tests were performed using the USP guidelines.[18,19] Nonetheless, the hardness and thickness tests were performed using Pharmatest PTB311E tablet hardness tester on 10 tablets taken randomly from each product.

RESULTS AND DISCUSSION

Development and validation of UV/Visible spectrophotometric analytical method

The UV/Visible spectrophotometer was used as an analytical tool for the quantification of paracetamol from the generic and innovator products. The results of the various validation parameters as obtained are shown in Table 1. The results demonstrated that the analytical method was linear, robust, accurate and precise as the values were found to be within the acceptable limits (±5%).

In vitro dissolution study

The release profiles of different paracetamol products (R, T1 and T2) in different pH conditions; 0.085 M hydrochloric acid pH 1.2, acetate buffer pH 4.5 and phosphate buffer pH 6.8 are depicted in Figure 1. In addition, the corresponding data is also shown in Table 2. The time required to release 25% ($t_{25\%}$), 50% ($t_{50\%}$) and 75% ($t_{75\%}$) of paracetamol from the various investigated products is shown in Table 3. The values of similarity factor, time required to release drug (%)

Table 1: Analytical method validation of paracetamol in 0.1 M sodium hydroxide solution.

Parameters		Acceptance criteria	Result
Linearity Correlation coefficient (r^2) ≥ 0.999 y-intercept ≤ 2%		Equation of straight line	y = 0.0715 x – 0.0027
		0.9999	
		0.251%	
Accuracy		≤ ± 2%	± 0.67 – 0.83%
Precision	Repeatability	RSD ≤ 2%	0.224%
	Immediate precision	RSD ≤ 2%	0.697%
Limit of detection		-	0.256 µg/mL
Limit of quantitation		-	0.775 µg/mL

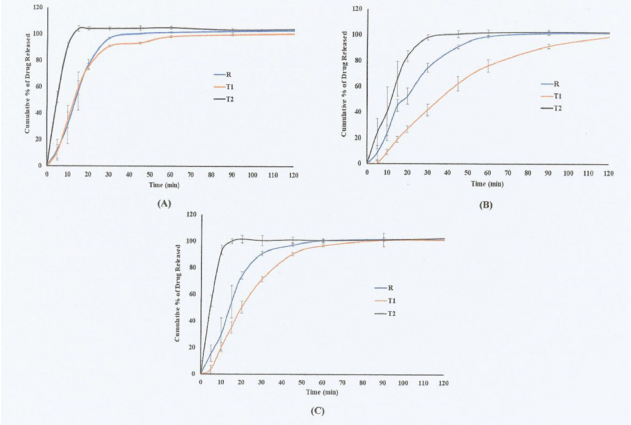

Figure 1: *In vitro* dissolution profiles of Reference (R), Test 1 (T1) and Test 2 (T2) products containing paracetamol: (A) 0.085 M hydrochloric acid, pH 1.2; (B) Acetate buffer, pH 4.5 and (C) Phosphate buffer, pH 6.8.

Table 2: *In vitro* dissolution results of Reference (R) and Test (T1 and T2) products.

Dissolution medium	Product	Mean percentage drug dissolved (%) (*n* = 6)								
		5 min	10 min	15 min	20 min	30 min	45 min	60 min	90 min	120 min
0.085 M hydrochloric acid pH 1.2	R	12.27 (20.61)	31.28 (25.73)	56.81 (25.46)	76.88 (18.77)	96.90 (4.02)	100.40 (0.78)	101.32 (0.30)	102.24 (0.53)	102.93 (0.81)
	T1	10.83 (22.79)	34.78 (14.68)	59.22 (10.18)	75.42 (6.90)	90.84 (2.33)	93.38 (0.70)	98.19 (0.64)	99.73 (0.88)	100.46 (0.71)
	T2	52.36 (12.88)	91.76 (4.74)	104.05 (1.65)	104.18 (2.11)	104.28 (1.20)	104.54 (1.19)	104.97 (1.58)	103.38 (1.07)	103.91 (1.11)
Acetate buffer pH 4.5	R	8.34 (19.65)	23.98 (22.96)	45.28 (13.38)	52.51 (8.97)	74.40 (8.52)	90.92 (3.70)	98.94 (1.48)	101.38 (0.86)	101.61 (1.34)
	T1	0.54 (90.93)	9.02 (18.28)	18.84 (11.27)	26.92 (9.02)	41.83 (6.23)	62.14 (7.28)	76.15 (7.19)	91.38 (5.16)	98.68 (1.72)
	T2	23.60 (21.76)	40.63 (28.63)	65.93 (28.84)	83.60 (16.01)	98.11 (4.48)	100.69 (2.21)	101.69 (2.63)	102.28 (2.23)	102.04 (1.64)
Phosphate buffer pH 6.8	R	15.54 (21.19)	30.14 (20.31)	54.47 (22.35)	74.09 (16.41)	90.91 (3.22)	97.19 (1.83)	100.58 (0.86)	101.78 (1.45)	101.57 (1.17)
	T1	3.63 (23.16)	20.29 (14.57)	35.03 (10.25)	50.42 (8.56)	71.58 (6.18)	90.47 (2.22)	96.81 (1.35)	101.02 (0.81)	101.22 (0.54)
	T1 (Paddle method)	13.05 (16.90)	61.55 (5.89)	93.72 (5.23)	99.58 (1.72)	104.44 (1.12)	105.28 (0.91)	105.92 (0.34)	107.54 (1.15)	108.05 (1.44)
	T2	55.06 (18.70)	93.15 (4.58)	100.06 (3.52)	101.59 (1.83)	100.47 (2.65)	101.06 (3.86)	100.69 (2.26)	101.39 (0.86)	102.63 (4.89)

The coefficient of variation (%) of each time point is shown in parentheses.

and the comparison of *in vitro* dissolution profile is highlighted in Table 4. Whilst comparing the dissolution profiles using similarity factor, coefficient of variation (COV) is reported as one of practical considerations recommended by various regulatory agencies with a COV value not exceeding 20% at earlier time points and not more than 10% for other time points.[5,7] However, as it is evident from Table 2, COV of a few time points selected in this study was higher than the recommended value. In order to acquire reliable result from a high variable dissolution data, model independent multivariate confidence region procedure (bootstrapping f_2 approach) was adopted to simulate the confidence interval for f_2 and the bias correction was estimated using the statistical distribution of the *in vitro* dissolution data.[5,8,20] Similarity was assumed when the 50% percentile is higher or at least equal to 50. The hardness of a tablet in each product had exhibited high standard deviations, which reflected a high variation in hardness of tablets under the same product. The fluctuations in the hardness value might be the factor behind the high COV values of dissolution data obtained for some time points. Apart from hardness, factors associated with manufacturing process such as compression force, humidity and the choice of excipients can also be accounted for such variations in the *in vitro* dissolution rate.[21] This issue is particularly pivotal to guarantee the desired therapeutic response of a drug within the stipulated time-frame for each patient, especially for a drug with low therapeutic index or controlled-release formulation.[22] Hence, it is imperative for a manufacturer to reduce intra- and inter-batch variations in their products to maintain or enhance the quality of the products in accordance with a recognized standard.

Table 3: Mean $t_{25\%}$, $t_{50\%}$ and $t_{75\%}$ values of Reference (R) and Test (T1 and T2) products (n = 6).

Dissolution medium	Product	Mean $t_{25\%}$ (min)	Mean $t_{50\%}$ (min)	Mean $t_{75\%}$ (min)
0.085 M hydrochloric acid pH 1.2	R	8.76 (18.59)	14.17 (19.14)	19.81 (20.63)
	T1	8.06 (8.65)	13.16 (9.35)	20.12 (11.12)
	T2	2.42 (14.26)	4.85 (13.98)	7.84 (8.03)
Acetate buffer pH 4.5	R	10.27 (12.89)	18.03 (16.10)	31.47 (10.89)
	T1	18.87 (7.71)	36.24 (7.18)	60.34 (13.12)
	T2	5.96 (25.76)	12.50 (25.25)	17.45 (23.69)
Phosphate buffer pH 6.8	R	8.49 (16.46)	14.65 (16.64)	20.48 (18.76)
	T1	11.63 (9.38)	20.10 (7.62)	32.63 (8.95)
	T2	2.34 (19.15)	4.65 (18.22)	7.48 (12.45)

The coefficient of variation (%) of each determination is shown in parentheses.

The dissolution profiles of T1 obtained using both USP Apparatus 1 and 2 in phosphate buffer are depicted in Table 2. Based on the results as shown in Table 2, paddle method provided higher dissolution rate of T1 compared to basket method and these findings were in agreement with those of a previously reported study.[23] Variabilities in the physical conditions of the test, operational differences, manufacturing processes or product handlings are the possible reasons behind the acquisition of two different data set for the same product using both dissolution apparatus under the similar dissolution conditions.[23] Table 4 represents the statistical results obtained using on the similarity factor and $t_{25\%}$, $t_{50\%}$ and $t_{75\%}$ approaches. Bootstrap approach was applied to re-evaluate *f2* value while one-way MANOVA followed by post hoc Tukey's test was used to analyse

Table 4: Comparison of dissolution profiles based on similarity factor approach and one-way MANOVA approach.

Dissolution medium	Comparisons	Similarity factor approach				Comparison of $t_{25\%}$, $t_{50\%}$, $t_{75\%}$ using one-way MANOVA approach			
		Observed f_2	Bootstrap mean	50% percentile	Similarity	$t_{25\%}$ (p-value)	$t_{50\%}$ (p-value)	$t_{75\%}$ (p-value)	Similarity
0.085 M hydrochloric acid pH 1.2	T1 versus R	72.31	65.29	53.04	Yes	0.489	0.596	0.978	Yes
	T2 versus R	15.05	15.09	12.80	No	0.000	0.000	0.000	No
Acetate buffer pH 4.5	T1 versus R	30.75	30.83	28.34	No	0.000	0.000	0.000	No
	T2 versus R	32.65	32.75	26.81	No	0.000	0.013	0.001	No
Phosphate buffer pH 6.8	T1 versus R	37.68	37.81	32.55	No	0.000	0.000	0.000	No
	T2 versus R	14.89	14.88	12.89	No	0.000	0.000	0.000	No

The number of bootstrap samples = 5000. The level of significance was considered when p-value ≤ 0.05.

Table 5: Physiochemical properties of Reference (R) and Test (T1 and T2) products.

Product	Diameter (mm) *N* = 10	Thickness (mm) *N*= 10	Hardness (N) *N* = 10	Friability* (%)	Weight variation (%) *N* = 20	Drug content (%) *N* = 10
R	12.92 (0.01)	4.72 (0.03)	103.98 (4.56)	0.03	0.67 (0.51)	99.89 (1.15)
T1	12.13 (0.04)	4.34 (0.06)	169.73 (19.34)	0.09	0.78 (0.49)	101.50 (2.32)
T2	12.87 (0.01)	4.79 (0.09)	177.87 (17.14)	0.17	1.21 (0.70)	100.49 (2.97)

The standard deviation of results was shown in parentheses.
*Sample of whole tablets corresponding to 6.5 g was taken for friability test.

the differences between $t_{25\%}$, $t_{50\%}$ and $t_{75\%}$ of R, T1 and T2. For bootstrap similarity factor approach, similarity between dissolution profiles is demonstrated when the 50% percentile is equal to or greater than 50.[7] For $t_{25\%}$, $t_{50\%}$ and $t_{75\%}$, similarity is indicated when *p*-value is greater than 0.05, showing the differences between the *in vitro* dissolution profiles are not statistically significant. It can be seen from Table 4 that only dissolution profiles of R and T1 in an acid medium demonstrated similarity.

As per the results shown in Table 4, bootstrap similarity factor was 53.04 for T1 in hydrochloric acid solution which indicates its similarity in terms of *in vitro* dissolution profile with that of innovator product (R). In addition, this finding was also supported by the p-values obtained during the comparison of $t_{25\%}$, $t_{50\%}$ and $t_{75\%}$ which were 0.489, 0.596 and 0.978 respectively. Since the p-values were found either higher or equal to 0.05, there was no statistically significant difference between the data being compared. The results presented in Table 4 demonstrated that T2 was not identical to the reference product in all dissolution media based on both approaches. Nevertheless, the mean $t_{25\%}$, $t_{50\%}$ and $t_{75\%}$ of T2 in all dissolution mediums were smaller than R (as illustrated in Table 3) indicating that T2 has a rapid dissolution compared to that of reference product suggesting that T2 is a better formulation compared to R as a fast dissolution rate is recommended for an immediate-release tablet product to initiate a prompt absorption and therapeutic response.[24] This interpretation cannot be constructed without knowing the $t_{25\%}$, $t_{50\%}$ and $t_{75\%}$ as *f2* value does not provide any information on this aspect. Nevertheless, time to release drug % ($t_{25\%}$, $t_{50\%}$ and $t_{75\%}$) parameter also possess some limitations. For instance, unlike similarity factor where the entire dissolution data at all-time points are used to evaluate similarity, time to release drug % ($t_{25\%}$, $t_{50\%}$ and $t_{75\%}$) merely considers a time point at once. Therefore, data at individual time points are not exclusive enough to adequately compare the two *in vitro* dissolution profiles. Therefore, it is recommended to utilize both similarity factor as well as $t_{25\%}$, $t_{50\%}$ and $t_{75\%}$ to compare dissolution profiles for better interpretation of results.

For other sets of data, both approaches highlighted similar results, indicating no similarity between the *in vitro* dissolution profiles under investigations. Based on these finding, it is obvious that both *in vitro* dissolution parameters namely similarity factor and time required to release % of drug were found essentially in a complete agreement indicating the similarity in dissolution profiles of generic and innovator products. The findings of this research through indicate the suitability of similarity factor alone in a reliable and robust tool to compare the dissolution profile of tablet products yet it may not be the case for every drug particularly with low therapeutic indices.[1] Therefore, it is proposed that similarity factor should be employed in combination with another parameter namely time required to release % of drug in the comparison of *in vitro* dissolution profiles.

Quality evaluation of tablets

The results of quality evaluation of various tablet products namely R, T1 and T2 employed in this study are shown in Table 5. It is evident from results that all products passed hardness, friability (<1%), weight variation (<5%) and drug content uniformity (90-110%) tests as per USP specifications. However, it was noticeable that the hardness of tablets irrespective of the product had high standard deviations which could be the potential cause of variations when different tablets under the same brand were subjected to *in vitro* dissolution study.

CONCLUSION

A robust and reliable comparison of *in vitro* dissolution profiles is a prerequisite amid the development of generic tablet, capsule or pellet-based product. The results of the present study highlight that similarity factor alone is predominantly capable for a commendable

comparison of *in vitro* dissolution data. However, the use of similarity factor alone may not be adequate to acquire a complete understanding about the release profiles of a drug at a particular time which could be crucial for potent drugs. Consequently, apart from similarity factor, other dissolution parameters such as time required to drug release ($t_{\%}$) at $t_{25\%}$, $t_{50\%}$ and $t_{75\%}$ should also be considered. Therefore, the findings of present study suggest the application of similarity factor in conjunction with another parameter namely time required to release drug 25% ($t_{25\%}$), 50% ($t_{50\%}$) and 75% ($t_{75\%}$) for a better and more therapeutically relevant comparison of the *in vitro* dissolution profiles of tablets during the formulation development process of a generic product.

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CONFLICT OF INTEREST

Authors declare that they have no conflict of interest in publishing this research work..

ABBREVIATIONS

***f_2*:** Similarity factor; **$t_{\%}$:** Time required to drug release; **R:** Reference product; **T:** Test product; **NaOH:** Sodium hydroxide; **FDA:** The food and drug administration; **ICH:** International Conference on Harmonization.

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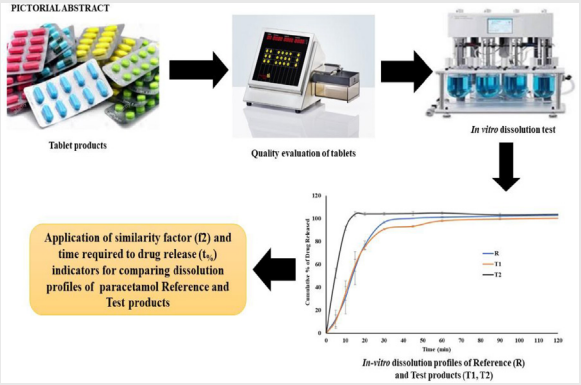
PICTORIAL ABSTRACT



SUMMARY

During the development of any generic product, it is prerequisite to compare its dissolution profiles with innovator products using similarity factor. The research question is whether similarity factor alone suffices to adequately compare the dissolution profiles or both similarity factor and time required to percentage drug release generate closely similar results. The Reference (R) and two generic paracetamol test products (T1 and T2), each containing 500 mg drug were subjected to dissolution studies at pH 1.2, 4.5 and 6.8. The resultant outcome confirmed that application of similarity factor alone may provide reliable results for comparison of dissolution profile. However, the time required to release $t_{25\%}$, $t_{50\%}$ and $t_{75\%}$ may be used along with similarity factor for better interpretation of *in vitro* dissolution results particularly for potent drugs.

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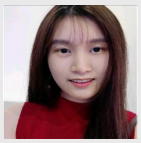

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