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Research Article

# STATISTICAL EVALUATION OF IN-VITRO DISSOLUTION PROFILES OF DIFFERENT BRANDS OF SIMVASTATIN 20 MG TABLETS AVAILABLE IN LOCAL MARKET OF KARACHI

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**ABSTRACT**

Objective: Simvastatin is lipid lowering agent that reduces the risk of total mortality and morbidity. For such a sensitive medicine, the availability of un-control brands, local and multinational is a point of thought. The objective of this study was to provide a comparative assessment of dissolution profile of six different brands of Simvastatin by applying dissolution profile comparison approach to check the possibility of interchangeability of different brands. Method: Dissolution was carried out with six units of each brand using USP apparatus-II (Paddle) at 37 ± 0.5°C in 900 ml phosphate buffer medium pH 7.0 with 0.5% SLS at 50 rpm. Samples were withdrawn from the dissolution medium at 5, 10, 15, 30, 45 and 60 min interval, and analyzed spectrophotometrically at 239 nm. Various statistical methods recommended by FDA such as Model-independent methods including difference $f_1$ and similarity factor $f_2$, Model dependent methods such as, First order, Hixson- Crowell and Weibull methods and One way ANOVA were used for the comparison of in vitro dissolution profiles.

Results: From results it was evaluated that all methods are useful and applicable in determination of similarity among all local test brands with innovator in dissolution and point up that model-independent method is simpler in interpretation in comparison with ANOVA and model-dependent method. ANOVA method presented similarity among all means of drug release with p-value >0.05. Model dependent methods are well explained and discriminative among various brands, Weibull is the best fit model on drug release data. The drug release mechanism was a detailed of Log dissolved amount of drug versus log time. Among all model dependent methods; Weibull is more sensitive and explanatory for release behavior and in determination between differences of two dissolution profiles.

Conclusion: On basis of evaluation it was concluded that a low cost brand $SIM^B$ can be useful in lipid lowering therapy.

**Keywords:** Dissolution comparison, Simvastatin tablets, Weibull model.

## INTRODUCTION

Simvastatin is a lipid reducing agent broadly used worldwide for the treatment of hypercholesterolemia as well as for minimizing the severity of chronic heart disease that causes morbidity and mortality [1]. Simvastatin is a Class II (low soluble and high permeable) drug according to BCS [2]. It is widely used drug included in statins which are HMG CoA reductase inhibitors. They are used for the lowering of cholesterol levels (low-density lipoprotein, or LDL) and triglycerides, while elevating levels of cholesterol (high-density lipoprotein, or HDL) in the blood [3].

In the case of poor soluble drug, dissolution may be the rate limiting step for absorption and an IVIVC may be expected. In the recent years, more emphasis has been placed on dissolution testing within the pharmaceutical industry and by the regulatory authorities [4].

The quality assurance of pharmaceutical products is a wide-ranging concept covering all issues that individually or collectively influence the quality of a product. In this regard, *in-vitro* dissolution tests are very essential to evaluate the lot-to-lot variation as well as brands-to-brands evaluation to ensure the quality and performance of the finished products. This is especially important when various different brands are available in the same market in order to make available safe and efficacious products to the patients at an affordable cost. As the generic products might have certain changes in the formulation ingredients, the source of active, the manufacturing process, the site of manufactures, batch size and scale-up of the manufacturing processes, it is necessary to have it pharmaceutically evaluated [5].

In case of poor soluble drugs like Simvastatin, that belongs to class II BCS classification, some unpredictable dissolution profile outcomes might be possible. In conventional compendial methods, various surfactants are mentioned such as SLS that might enhance the solubility and improve the dissolution of poor soluble particles. FDA has developed the guidelines for immediate dosage form in which statistical methods are recommended for comparing dissolution profiles [6] these test included model independent and dependent approaches.

The aim of this study was to establish the dissolution profiles of six brands of 20 mg Simvastatin tablets, available in the local market of Karachi (Pakistan), in the pharmacopieal dissolution medium i.e, pH 7.0 buffer with 0.5% SLS. In order to evaluate similarity in dissolution and to establish the dissolution conditions for Simvastatin, assessment in pharmaceutical immediate release tablets was conducted and six different commercial brands were compared, using $SIM^A$ as reference and $SIM^B$, $SIM^C$, $SIM^D$, $SIM^E$ and $SIM^F$ as test formulations. Different statistical models such as model independent approach including $f_1$, $f_2$ test and one way ANOVA was used in the present study. Moreover, model-dependent approaches which are recommended for IR tablets such as first order, Hixson-Crowell and Weibull models were also used to evaluate the best fit model.

## MATERIALS AND METHODS

Simvastatin was kindly gifted by Barret Hodgson Pvt. Ltd, Karachi, Sodium dihydrogen phosphate, NaOH, sodium lauryl sulphate (Sigma-Aldrich, Germany), distilled water freshly prepared.

### Instrumentation

Erweka DT600, Shimadzu-UV visible 1800 spectrophotometer, Sartorius analytical balance, pH meter, Jenway (Germany).

### Physical Parameters

Physical examination performed on twenty units of each brand for weight variation, Diameter, Thickness and 10 units for Hardness.

### Cost Comparison

The differences in retail price of all test brands were compared with innovator price by following formula:

(Price of innovator - price of test) ÷ Price of innovator × 100 [7]

### Dissolution Medium

Buffer solution of pH 7.0 has been prepared by dissolving 8.28 g of sodium dihydrogen phosphate in 6000 ml of distilled water and pH

adjusted to 7.0 by 10% w/v sodium hydroxide and finally adding 0.5% w/v sodium lauryl sulphate [3].

**In-vitro dissolution test**

Dissolution test was carried out on six different brands of Simvastatin tablets (20 mg).The reference was coded $SIM^A$ and five test brands as $SIM^B$, $SIM^C$, $SIM^D$, $SIM^E$ and $SIM^F$. the test was carried out with six units of each brand using USP apparatus-II (Paddle) at 37 ± 0.5°C in 900 ml phosphate buffer medium pH 7.0 with 0.5% SLS at 50 rpm. Samples of 10 mL were withdrawn from the dissolution medium at 5, 10, 15, 30, 45 and 60 min intervals, followed by immediate replacement of fresh dissolution medium for the acquisition of sink condition. The sample was filtered through Whatman filter No. 41 and analyzed spectrophotometrically at 239 nm.

**Preparation of standard solution**

Simvastatin (reference powder) equal to 10 mg was accurately weighed and dissolved in 10 ml of ethanol. From this stock solution, 1ml was diluted up to 50 ml with dissolution medium, making the final concentration equivalent to 20µg/ml.

**Dissolution test comparison**

**Model independent approach**

A simple model independent approach was used in the present investigation that was difference factor ($f_1$) and similarity factor ($f_2$). The $f_1$ values should be close to 15, and $f_2$ values should be close to 100 [6].

$f_1 = \{[\sum_{t=1}^{n}| R_t - T_t |]/[\sum_{t=1}^{n} R_t ]\}* 100$

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

**Model dependent approach**

Simvastatin release kinetics was analyzed by different mathematical models included first order, Weibull and Hixson-Crowell considering the amounts of drug released up to 60 min. (Table 1) [8,9,10]

The approach for plotting the graph was:

1) Log cumulative percentage (%) drug remaining versus time (first- order kinetic model);

2) Cube root of drug % remaining in matrix versus time (Hixson-Crowell cube root law); and

3) Log dissolved amount of drug versus log time (Weibull model). [11,12]

**Table 1: Dissolution Model applied**

| Model | Equation |
|---|---|
| First order | $\ln Q_t = \ln Q_o - K_1 t$ |
| Hixson-Crowell | $W_o^{1/3} - W_t^{1/3} = K_s t$ |
| Weibull | $\log [- \ln (1-m)] = \beta \log (t-T_i) - \log \alpha$ |

$Q_t$: amount of drug released in time t

$Q_o$: initial amount of drug in tablet

$K_1$, $K_s$: release rate constants

m: accumulated fraction of the drug

β: shape parameter

α: scale parameter

$T_i$: location parameter

**Statistical Analysis**

one-way ANOVA was applied using Microsoft excel 2007.

**RESULTS**

The aim of the present work, as a surveillance study, was to assess the product quality of different brands of Simvastatin tablets (20mg) available in the local market to determine the appropriateness of their inter-changeability. Table 2 shows the six brands of Simvastatin tablet with their label information indicating the difference of prices, expressed in percentage in comparison to the innovator.

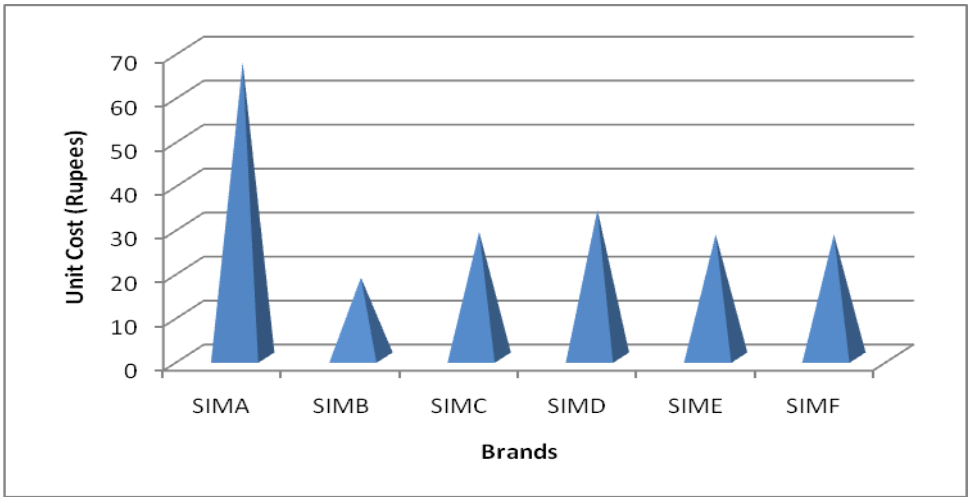


**Fig. 1: Unit Cost of various brands**

**Table 2: Label Information of Six Brands of Simvastatin Tablets (20mg)**

| S. No. | Brand code | Batch No. | Mfg. date | Exp. date | Price/10 units PKR | Price difference with innovator |
|---|---|---|---|---|---|---|
| 1 | **$SIM^A$** | B523 | 9-Mar | 11-Mar | 671.67 | innovator |
| 2 | **$SIM^B$** | 570 | 10-Mar | 12-Mar | 182 | 72.90 |
| 3 | **$SIM^C$** | 1177 | 9-Sep | 11-Sep | 286 | 57.42 |
| 4 | **$SIM^D$** | MT662 | 10-Dec | 12-Dec | 335.83 | 50.00 |
| 5 | **$SIM^E$** | OA024 | 10-Jan | 12-Jan | 280 | 58.31 |
| 6 | **$SIM^F$** | 10 | 9-Apr | 11-Apr | 280 | 58.31 |

**Physical parameters**

To compare the pharmaceutical equivalence among test brands and innovator brand, different physical and chemical parameters were performed according to USP-32 NF-27 (see, Table 3).

**Comparison of dissolution profile**

The dissolution profiles of the six products were tested according to the method described in the USP-32 (Figure 2).

The FDA, US suggest that the model-independent and model-dependent approaches could be used for the authentic evaluation of dissolution profiles of various brands. Table 4, 5, 6 are showing model independent, model dependent and one way ANOVA results of various brands of Simvastatin 20 mg.

Linearization of dissolution profiles of various brands (Table 5) that characterized similarity among all brands and plots for different models are shown in figure 3-5

**Table 3: physical parameters of various brands of Simvastatin 20 mg**

| S. No. | Brand Code | Average weight ±S.D mg | Diameter±S.D mm | Thickness±S.D mm | *Hardness±S.D kg |
|---|---|---|---|---|---|
| 1 | **SIM$^A$** | 210±1.649 | 11.02 ±0.056 | 4.0311±0.0022 | 5.865±0.138 |
| 2 | **SIM$^B$** | 258.15±4.068 | 10.028±0.0025 | 4.03325±0.004 | 5.1425±0.049 |
| 3 | **SIM$^C$** | 163.5±3.425 | 9.0215±0.006 | 4.032±0.0025 | 10.34±0.287 |
| 4 | **SIM$^D$** | 206.75±2.672 | 11.02175±0.002 | 4.032±0.0025 | 2.4785±0.093 |
| 5 | **SIM$^E$** | 218.68±1.993 | 11.0175±0.006 | 4.04125±0.0022 | 7.278±0.041 |
| 6 | **SIM$^F$** | 187.4±3.10 | 8.0151±0.00071 | 4.042±0.0025 | 4.32±0.0410 |

(Result based on n=20 and * n=10)

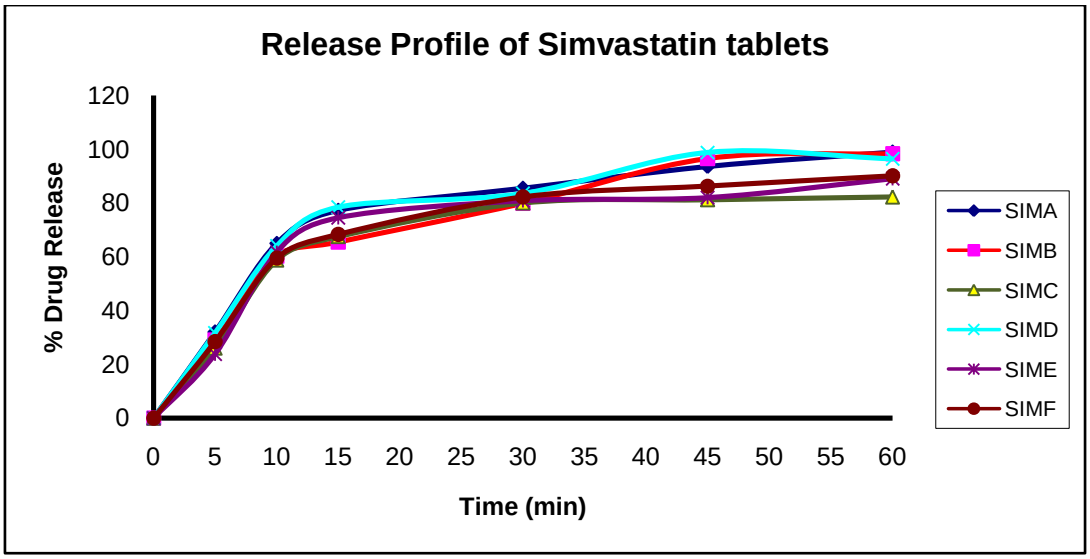


**Fig. 2: Release kinetics of six brands in pH 7.0 buffer with 0.5% SLS**

Result based on average of (n=6)

**Table 4: $f_1$ and $f_2$ value for each formulation**

| Formulation | $f_1$ | $f_2$ |
|---|---|---|
| **SIM$^A$** | Innovator | Innovator |
| **SIM$^B$** | 5.021 | 61.2 |
| **SIM$^C$** | 12.475 | 49.36 |
| **SIM$^D$** | -0.1327 | 78 |
| **SIM$^E$** | 8.891 | 56.02 |
| **SIM$^F$** | 8.25 | 58.69 |

**Table 5: Linearization of Simvastatin dissolution profiles using model dependent method**

| Dissolution models | SIM$^A$ | SIM$^B$ | SIM$^C$ | SIM$^D$ | SIM$^E$ | SIM$^F$ |
|---|---|---|---|---|---|---|
| First order K | 0.09 | 0.073 | 0.066 | 0.09 | 0.074 | 0.072 |
| Ratio K (test/Std) | | 0.811 | 0.733 | 1.232 | 1.121 | 0.8 |
| $R^2$ | 0.9517 | 0.9546 | 0.7381 | 0.9461 | 0.7985 | 0.8932 |
| Hixson Crowell K | 0.023 | 0.020 | 0.019 | 0.023 | 0.021 | 0.020 |
| Ratio K (test/Std) | | 0.883963 | 0.947896 | 1.193453 | 0.910285 | 0.971084 |
| $R^2$ | 0.8784 | 0.8999 | 0.5849 | 0.8707 | 0.6920 | 0.7923 |
| Weibull $R^2$ | 0.9926 | 0.9744 | 0.9935 | 0.9802 | 0.9912 | 0.9994 |
| β | 0.488 | 0.619 | 0.298 | 0.514 | 0.301 | 0.408 |
| Ratio β (test/Std) | | 1.267753 | 0.482345 | 1.721012 | 0.586684 | 1.354773 |
| Td (min) | 9.449 | 12.544 | 11.832 | 9.585 | 9.752 | 11.669 |
| α | 2.231 | 3.963 | 1.784 | 2.379 | 1.606 | 2.233 |
| $T_{50\%}$ (min) | 6.709 | 8.403 | 6.913 | 6.827 | 6.363 | 7.428 |

**Table 6: Results of One way ANOVA**

| *Source of Variation* | *SS* | *df* | *MS* | *F* | *P-value* | *F crit* |
|---|---|---|---|---|---|---|
| Between Groups | 441.3233 | 5 | 88.26467 | 0.152993 | 0.977518 | 2.533555 |
| Within Groups | 17307.63 | 30 | 576.9209 | | | |
| Total | 17748.95 | 35 | | | | |

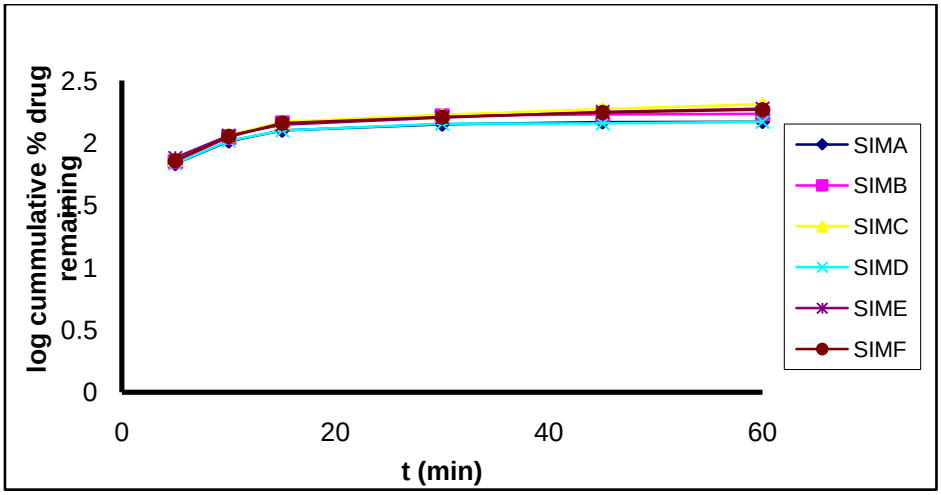


**Fig. 3: First order plots for SIM brands**

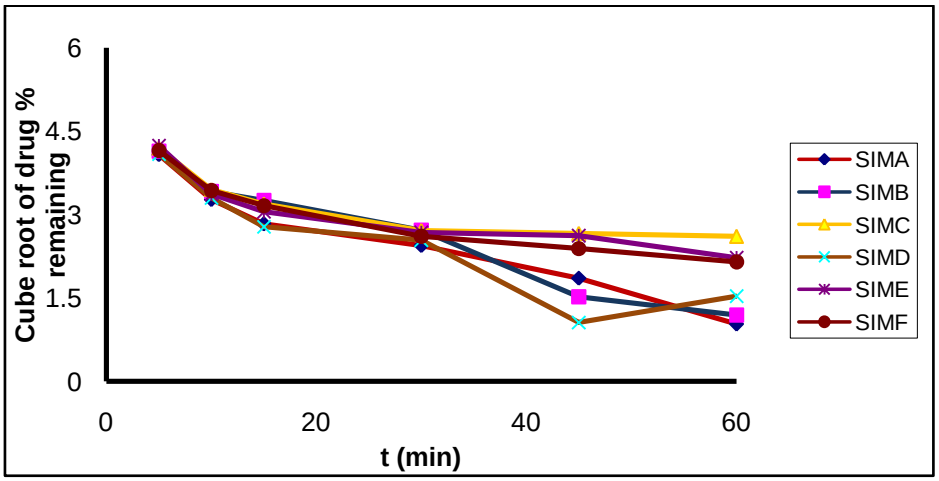


**Fig. 4: Hixson Crowell plots for SIM brands**

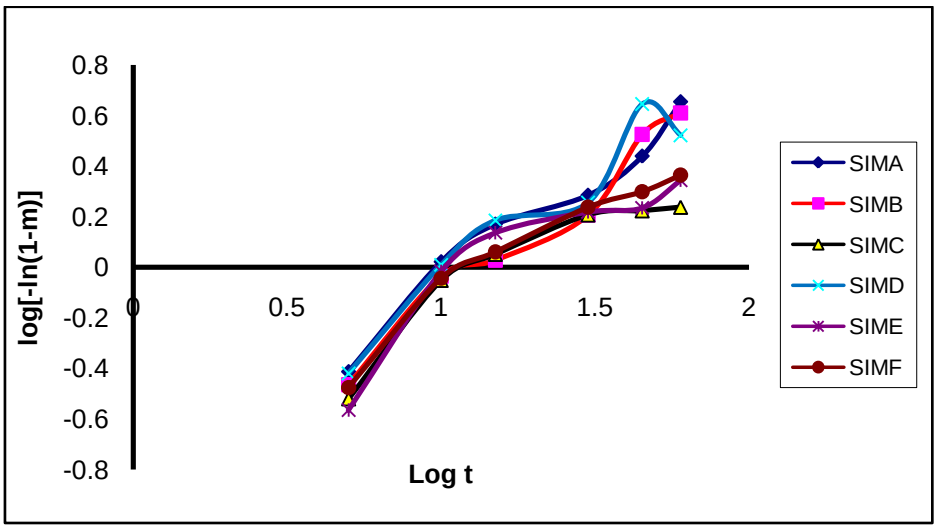


**Fig. 5: Weibull plots for SIM brands**

**DISCUSSION**

Pakistan is a developing country where 70-80 % of the population could not be able to pay for costly medication. In cost analysis of various brands it was determined that the innovator is expensive 50% more than test brands. The lowest price brand was $SIM^B$ i.e. Rs 182 per 10 units (see Table 2) and showing approximately the same release kinetic means to be used inter-changeably.

Prior to dissolution testing, analysis of physical parameter is an important to perform for the establishment of a meaningful correlation between physical characterizes of a product and *in vitro* release of drug that helps in understanding the *in vivo* bioavailability of the drug. In a number of published research reports, the physicochemical parameters were mentioned as a primarily important for establishing a stable and effective drug product [13, 14, 15, 16, 17, 18, 19, 20]. According to the results tested brands were similar to the innovator (table 3). Model independent method based on $f_1$ and $f_2$ values indicated this approach to be expedient for application for establishing equivalence among various brands, innovator brand considered as reference owing all quality attributes, test brands marketed by local manufacturer and their quality must be verified. Simvastatin is a poor water soluble drug so simple aqueous buffer medium like pH 1.2, 4.5 and 6.8 are not giving such a dissolution profiles as in medium pH 7.0 with 0.5% SLS (figure 2). In model dependent methods, Among all brands Weibull model fits best model to the dissolution data, considered high determination coefficient ($R^2$) whereas first order and Hixson Crowell failed to be fit (< 0.98). Weibull described dissolution profile in terms of shape and scale parameter. β represented shape parameter of curve as exponential (β=1), S-shaped with upward curvature followed by turning point (β>1) and steeper initial slope than is consistent with exponential (β<1). Calculated weibull β parameter was <1 for all brands specified a parabolic curve with steeper initial slope than is consistent with the exponential was shown in Table 5, β for all brands were not so different except $SIM^C$ and $SIM^F$ were 0.298 and 0.301. The time parameter, $T_d$ can be calculated from α and β parameters ($\alpha = (td)^{\beta}$) and represents the time interval required to dissolve 63.2% of the drug [8]. $T_d$ for all brands were not so different with innovator brand, there is only 2-3 min difference observed. Weibull is considered a good model in determination of difference among various brands. Various studies have done on dissolution comparison of poor soluble drugs indicated that Weibull Model is better to characterize the dissolution kinetics [21, 22]. One-way (ANOVA) applied to compare mean percentage DR of six brands and evaluated the variances between groups and within groups 0.05 level of significance (Table 6). It is concluded that no significant variation found between and within different brands, calculated F-value (0.152) is less than tabulated F-value (2.533); and ($P = 0.977$).

**CONCLUSION**

The purpose of this study was to determine similarity of various brands of Simvastatin by applying different comparison approaches with the intent to investigate several methods. Each method was applicable and useful that used for the comparison of dissolution profiles. The model independent approach was sensitive to the number of dissolution time points. Model dependent approach explained the release kinetics and parameters of the Weibull model that suggest a meaningful comparison of level ($T_d$) and homogeneity in profile shape. Although $f_1$ and $f_2$ are simpler approaches, but using model-dependent models could determine the differences between the profiles.

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