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# Comparison of in vitro dissolution profiles by ANOVA-based, model-dependent and -independent methods

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**Abstract**

In this study, the aim was to apply different comparison methods to dissolution profiles of immediate release commercial film-coated tablets of naproxen sodium in order to (1) evaluate each method in terms of easy application and usefulness and (2) identify the advantages and disadvantages of each method. Dissolution testing was conducted using the USP monograph of naproxen sodium. The applied methods for the comparison of in vitro dissolution profiles are ANOVA-based methods, model-dependent methods, and model-independent methods including difference factor, $f_1$, and similarity factor, $f_2$. All the methods appear to be applicable and useful in comparing dissolution profiles. The results show that ANOVA-based methods and model-dependent methods are more discriminative than the $f$-factors. $f$-Factors seem to be easier to apply and interpret; only one value is obtained to describe the closeness of the two dissolution profiles. However, a last point for dissolution had to be determined, since the values of the $f$-factors depend on this point. The application and evaluation of model-dependent methods are more complicated; these methods present an acceptable model approach to the true relationship between percent dissolved and time variables, including statistical assumptions which could be checked. Dissolution profiles can be tested for differences in both level and shape by ANOVA-based methods and these methods provide detailed information about dissolution data which can be useful also in formulation development to match release to a reference product. 

*Keywords:* Comparison of dissolution profiles; ANOVA-based methods; Model-dependent methods; Model-independent methods; Difference factor; Similarity factor

## 1. Introduction

Drug absorption from solid dosage forms after oral administration depends on the release of the drug substance from the drug product, the dissolution or solubilization of the drug under physiological conditions, and the permeability across the gastrointestinal tract. Because of the critical nature of the first two of these steps, in vitro dissolution may be relevant to the prediction of in vivo performance. Based on this general consideration,

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in vitro dissolution tests for immediate release solid oral dosage forms are used: (1) to assess the lot-to-lot quality of a drug product; (2) to assess the stability of the drug product; (3) to ensure continuing product quality and performance after certain changes, such as changes in the formulation, the manufacturing process, the site of manufacture, and the scale-up of the manufacturing process; and (4) to develop new formulations. In formulation development, dissolution testing can aid in the selection of excipients, help optimize the manufacturing process, and enable formulation of the test product to match the release of the reference product (Carrico, 1996; Shah et al., 1997).

The dissolution method and specification are set by considering the solubility, permeability, dissolution, and pharmacokinetics of the drug substance. Three categories of dissolution test specification for immediate release products are described in the guidance provided by the Center for Drug Evaluation and Research at the Food and Drug Administration (FDA, 1997a): (1) single-point specifications, (2) two-point specifications, and (3) dissolution profile comparison. Though this 'point estimate' approach is suitable for drug products containing drug substances with high solubility-high permeability, it may not be adequate for low solubility drug substances or products with modified release characteristics. In these situations sometimes the drug products with inherently different dissolution profiles may comply with the point estimate given as pharmacopeia standard. This in turn may inadvertently lead to the declaration of similar dissolutions. The dissolution profile comparison seems to be more precise than the point estimate approach to characterize the drug product (Sathe et al., 1996; Shah et al., 1999).

The methods for the comparison of in vitro dissolution profiles can be classified into three groups: (1) the methods based on analysis of variance (ANOVA) (Mauger et al., 1986; Polli et al., 1997), (2) model-dependent methods (Sathe et al., 1996; Polli et al., 1997; Shah et al., 1997), and (3) model-independent methods (Podczeck, 1993; Moore and Flanner, 1996; Polli et al., 1997; Shah et al., 1997, 1998). ANOVA-based methods do not rely on curve fitting procedures and the dissolution data are used in their native form or as a simple transform and the analysis is capable of showing differences between profiles in level and shape. The latter characteristic is especially important with respect to learning about differences in the dissolution mechanism. The characterization as model-dependent method or model-independent method depends on the values which are used to perform the calculation. A model-independent method uses the dissolution data in their native form. The model-dependent methods, however, are based on different mathematical functions, which describe the dissolution profile. Once a suitable function has been selected, the dissolution profiles are evaluated depending on the derived model parameters.

The objectives of this work are to apply different profile comparison methods to the dissolution data of immediate release commercial film-coated tablets of naproxen sodium in order to (1) evaluate each method in terms of being easily applied and meaningful and (2) identify the advantages and disadvantages of each method.

## 2. Materials and methods

### 2.1. Materials

The following commercial film-coated tablets of naproxen sodium were tested: reference, lot no. 9904007 (manufacturer R); test 1, lot no. 990302 (manufacturer 1); test 2, lot no. 99040615 (manufacturer 2); test 3, lot no. 9712159 (manufacturer 3); test 4, lot no. 990101 (manufacturer 4); test 5, lot no. 9805041 (manufacturer 5). The labeled amount of the drug substance is 275 mg per tablet. All other chemicals and reagents were analytical grades.

### 2.2. Dissolution testing

Dissolution studies on six commercially available film-coated tablets of naproxen sodium were conducted in USP Apparatus 2 (paddle method) (Aymes D96D, Istanbul, Turkey) with six replicates, according to the USP monograph (US Pharmacopeia 23, 1997, Sixth Supplement). The

dissolution medium was 900 ml of phosphate buffer (pH 7.4). The paddle rotation speed was kept at 50 rpm. In all experiments, 5 ml of dissolution sample was withdrawn at 5, 10, 15, 20, 30, and 45 min and replaced with an equal volume of the fresh medium to maintain a constant total volume. Samples were assayed by UV spectrophotometry at 329 nm (Shimadzu UV-1202, Tokyo, Japan). Cumulative percentages of the drug dissolved from the tablets were calculated.

### 2.3. Applied methods to compare dissolution profiles

#### 2.3.1. ANOVA-based methods

This study was based upon repeated measures designs. In this model, the percents dissolved were dependent variable and time was the repeated factor. Sources of variation were the time, drug product, and interaction between time and drug product (time × drug product). Firstly, a multivariate approach (MANOVA) was applied. It tested whether there were significant differences among the percents dissolved at each time level without considering the drug products (time), and among the drug products regarding the percent dissolved depending on time (time × drug product), i.e. whether the dissolution profiles of the drug products were parallel. The Wilks lambda statistic was preferred to obtain $P$-values in MANOVA (Kanık, 1999). For the second step, a single group univariate repeated measures analysis (univariate ANOVA) was applied. This time, the percents dissolved were tested separately at each time point to see if there were differences among the drug products (drug product). Then post hoc procedures were applied to determine whence the differences arose: pairwise comparisons as test product against reference product were performed by multiple comparisons using Dunnett's $t$-test (two-sided) and repeated contrasts were applied separately to each drug product for the comparison of percents dissolved at the sequential times. Contrast is also a type of multiple comparison and a weighted combination of means (Lomax, 1998). For these ANOVA-based methods, SPSS 8.0 for Windows (SPSS, Chicago, IL) was employed.

#### 2.3.2. Model-dependent methods

The mathematical models, shown in Table 1, were fitted to individual dissolution data with the non-linear regression module of Statistica 5.0 for Windows (Statsoft, Tulsa, OK). In non-linear regression analysis, the Quasi-Newton and Simplex methods minimized the least squares. The model parameters with their standard errors and descriptive statistics of regression for each model were estimated by the non-linear regression module of Statistica. Depending on these estimations, suitable mathematical models to describe the dissolution profiles were determined. The derived parameters of the models were employed for the pairwise comparison of the profiles as reference-test product using $t$-test (Bolton, 1997). As regards applying model-dependent methods, the percents dissolved were decreased to maximum 100% by a multiplier considering the highest percent dissolved in Table 2.

#### 2.3.3. Model-independent methods

The description of the in vitro dissolution profiles by using model-independent methods includes the calculation of mean dissolution time (MDT) from the dissolution profile, mean residence time (MRT) from the residence profile, or area under dissolution curve. In vitro dissolution profiles can statistically be compared through these parameters (Podczeck, 1993; Polli et al., 1997). In this

Table 1
Applied mathematical models to the dissolution data of naproxen sodium tablets[a]

| Function | Equation |
|---|---|
| First-order | $\%diss = 100[1-e^{-kt}]$ |
| Hixson-Crowell | $\%diss = 100\left[1-\left(1-\frac{kt}{4.6416}\right)^3\right]$ |
| Higuchi | $\%diss = kt^{0.5}$ |
| Weibull | $\%diss = 100[1-e^{-(t/T_d)^\beta}]$ |
| Logistic | $\%diss = 100\left[\frac{e^{(\alpha+\beta\log t)}}{1+e^{(\alpha+\beta\log t)}}\right]$ |

[a] $\alpha$, scale factor; $\beta$, shape parameter; %diss, percent dissolved at time $t$; $k$, dissolution rate constant; $T_d$, time at which 63.2% of the material is dissolved.

Table 2
Dissolution data and descriptive analysis of naproxen sodium tablets ($n = 6$)

| Time | Product | Mean, % | S.E. | 95% CI for mean | | Min. | Max. |
|---|---|---|---|---|---|---|---|
| | | | | Lower bound | Upper bound | | |
| 5 min | Reference | 24.7 | 1.24 | 21.5 | 27.9 | 20.2 | 28.7 |
| | Test 1 | 29.8 | 1.22 | 26.6 | 32.9 | 26.1 | 33.2 |
| | Test 2 | 29.7 | 2.29 | 23.8 | 35.6 | 22.8 | 37.5 |
| | Test 3 | 29.0 | 1.11 | 26.2 | 31.9 | 26.6 | 32.7 |
| | Test 4 | 24.1 | 0.80 | 22.0 | 26.1 | 22.4 | 27.7 |
| | Test 5 | 16.7 | 1.51 | 12.8 | 20.5 | 12.8 | 37.5 |
| 10 min | Reference | 53.6 | 1.88 | 48.8 | 58.4 | 45.9 | 60.2 |
| | Test 1 | 61.4 | 1.38 | 57.8 | 64.9 | 56.4 | 64.3 |
| | Test 2 | 68.3 | 2.88 | 60.9 | 75.7 | 59.9 | 76.8 |
| | Test 3 | 60.1 | 1.87 | 55.3 | 64.9 | 53.0 | 66.3 |
| | Test 4 | 55.8 | 1.49 | 51.9 | 59.6 | 50.8 | 61.4 |
| | Test 5 | 48.1 | 1.75 | 43.6 | 52.6 | 42.8 | 52.2 |
| 15 min | Reference | 75.5 | 2.36 | 69.4 | 81.5 | 65.9 | 82.9 |
| | Test 1 | 85.5 | 1.48 | 81.7 | 89.3 | 80.5 | 88.9 |
| | Test 2 | 93.8 | 2.06 | 88.5 | 99.1 | 87.6 | 99.2 |
| | Test 3 | 86.3 | 1.78 | 81.8 | 90.9 | 80.5 | 93.3 |
| | Test 4 | 84.3 | 2.52 | 77.8 | 90.7 | 74.8 | 90.6 |
| | Test 5 | 68.9 | 2.10 | 63.5 | 74.3 | 62.3 | 74.8 |
| 20 min | Reference | 89.1 | 2.22 | 83.4 | 94.8 | 79.7 | 93.7 |
| | Test 1 | 98.5 | 1.16 | 95.5 | 101.5 | 94.3 | 101.7 |
| | Test 2 | 104.0 | 0.75 | 102.1 | 105.9 | 102.0 | 106.5 |
| | Test 3 | 102.2 | 1.48 | 98.4 | 106.0 | 97.8 | 108.4 |
| | Test 4 | 100.0 | 1.96 | 95.0 | 105.1 | 92.8 | 104.2 |
| | Test 5 | 83.4 | 1.61 | 79.3 | 87.6 | 77.5 | 88.5 |
| 30 min | Reference | 97.6 | 1.07 | 94.8 | 100.3 | 95.0 | 100.1 |
| | Test 1 | 104.5 | 0.70 | 102.7 | 106.3 | 101.3 | 106.2 |
| | Test 2 | 106.0 | 0.32 | 105.2 | 106.8 | 104.9 | 107.0 |
| | Test 3 | 112.0 | 0.96 | 109.5 | 114.5 | 109.4 | 115.6 |
| | Test 4 | 109.1 | 1.18 | 106.1 | 112.1 | 107.1 | 114.1 |
| | Test 5 | 98.9 | 1.10 | 96.1 | 101.8 | 96.6 | 103.7 |
| 45 min | Reference | 99.6 | 0.94 | 97.2 | 102.0 | 95.8 | 102.9 |
| | Test 1 | 104.8 | 0.76 | 102.9 | 106.8 | 101.5 | 106.6 |
| | Test 2 | 106.4 | 0.45 | 105.3 | 107.6 | 104.9 | 107.9 |
| | Test 3 | 112.6 | 1.08 | 109.9 | 115.4 | 110.0 | 117.5 |
| | Test 4 | 109.4 | 1.12 | 106.5 | 112.2 | 107.4 | 114.1 |
| | Test 5 | 101.0 | 0.88 | 98.8 | 103.3 | 97.7 | 104.3 |

study, as model-independent approaches, two fit factors that compare the dissolution profiles of a pair of drug products were applied to the dissolution data. These fit factors directly compare the difference between percent drug dissolved per unit time for a test and a reference product. The fit factors are denoted $f_1$ (difference factor), and $f_2$ (similarity factor) and are defined by Eqs. (1) and (2) (Moore and Flanner, 1996):

$$f_1 = \left\{ \frac{\sum_{t=1}^{n} |R_t - T_t|}{\sum_{t=1}^{n} R_t} \right\} \times 100 \quad (1)$$

$$f_2 = 50 \log\left\{ \left( 1 + \frac{1}{n} \sum_{t=1}^{n} (R_t - T_t)^2 \right)^{-0.5} \times 100 \right\} \quad (2)$$

where $n$ is the number of dissolution sample times, and $R_t$ and $T_t$ are the individual or mean

percent dissolved at each time point, $t$, for the reference and test dissolution profiles, respectively.

## 3. Results and discussion

The dissolution results as the means of percents dissolved versus time and descriptive analyses for commercially available tablets of naproxen sodium are given in Table 2. The in vitro dissolution profiles of the tablets are shown in Fig. 1. Each data point represents a mean of six measurements for each product. All drug products complied with the dissolution specification, $Q$, stated in the USP (US Pharmacopeia 23, 1997, Sixth Supplement) as dissolution not less than 80% of the labeled amount of naproxen sodium within 45 min.

### 3.1. ANOVA-based methods

Since the data were collected as repeated measurements over time on the same experimental unit, a repeated measures design was applied. When compared to Student's $t$- and paired $t$-tests, the major advantage of repeated measures designs is increased precision because of the smaller Type I error. Both a univariate approach (univariate ANOVA) and a multivariate approach (MANOVA) can be used for repeated measures analysis. In general, the univariate analysis is more informative and its interpretation is easier, while the multivariate analysis requires a simple transformation on the repeated measures such as the formation of sequential or non-sequential difference variables and this can make the interpretation difficult. Therefore, if an overall difference is found between the treatments or conditions as a result of MANOVA, univariate ANOVA and post hoc procedures are applied to find the source of difference (Johnson and Wichern, 1982; Stevens, 1986).

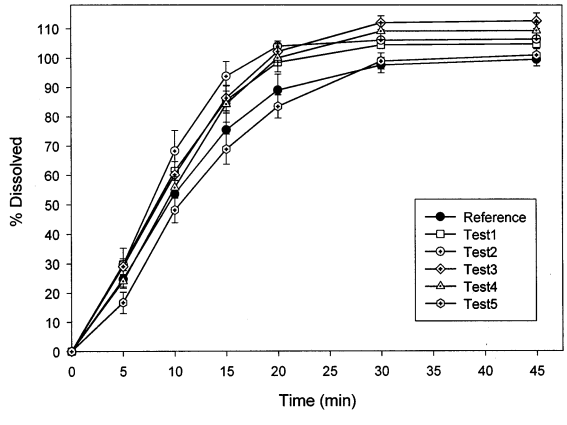


Fig. 1. Mean ($n = 6$) dissolution profiles of naproxen sodium tablets.

According to the results of MANOVA, the percents dissolved were found to be significantly different at each time level ($P < 0.001$) and among the drug products ($P < 0.001$), implying the significant time × drug product interaction, i.e. that the dissolution profiles were not parallel (Fig. 1). This interaction indicated that the mean difference of percent dissolved between two drug products was not constant at any two points of time considered. When Fig. 1 and Table 2 were examined together, it was seen that the mean difference of percent dissolved between test 5 and reference was $\sim 8.0\%$ at 5 min, while it was $\sim 1.3\%$ at 30 min. While the difference between test 1 and test 2 at 5 min was almost none, it increased to 6.9% at 10 min and decreased to 1.6% at 45 min. The change of the percents dissolved between any pair of the tested drug products at the time points considered in this way shows that the dissolution profiles are not parallel. The results of univariate ANOVA also showed that the drug products were significantly different in terms of percent dissolved at each time point ($P < 0.001$).

As for post hoc procedures, the results of pairwise comparisons of test products against reference by Dunnett's $t$-test are given in Table 3. It was found that the percents dissolved of test 5 and reference were not significantly different at the time points after 5 min, while test 1 and test 2 were significantly different from reference at the same time points. For test 3 and test 4, significant differences were observed at the time points after 10 min. As regards the repeated contrasts, the differences between the means of percents dissolved (Table 2) were tested in terms of significance at the sequential time levels within each drug product. The time levels were 5 versus 10

Table 3
Multiple comparisons of test products against reference product by Dunnett's $t$-test (two-sided) ($n = 6$)

| Time | $I$ | $J$ | Mean[a] difference ($I-J$) | Significance | 95% CI | |
|---|---|---|---|---|---|---|
| | | | | | Lower bound | Upper bound |
| 5 min | Test 1 | Reference | 5.06 | 0.074 | −0.36 | 10.47 |
| | Test 2 | Reference | 4.94 | 0.083 | −0.47 | 10.35 |
| | Test 3 | Reference | 4.29 | 0.158 | −1.12 | 9.70 |
| | Test 4 | Reference | −0.67 | 0.997 | −6.09 | 4.74 |
| | Test 5 | Reference | −8.08** | 0.002 | −13.50 | −2.67 |
| 10 min | Test 1 | Reference | 7.77* | 0.033 | 0.50 | 15.05 |
| | Test 2 | Reference | 14.66*** | 0.000 | 7.38 | 21.93 |
| | Test 3 | Reference | 6.48 | 0.094 | −0.80 | 13.76 |
| | Test 4 | Reference | 2.16 | 0.894 | −5.12 | 9.44 |
| | Test 5 | Reference | −5.48 | 0.192 | −12.76 | 1.80 |
| 15 min | Test 1 | Reference | 10.00** | 0.008 | 2.19 | 17.80 |
| | Test 2 | Reference | 18.29*** | 0.000 | 10.48 | 26.10 |
| | Test 3 | Reference | 10.87** | 0.004 | 3.06 | 18.68 |
| | Test 4 | Reference | 8.78* | 0.023 | 0.97 | 16.59 |
| | Test 5 | Reference | −6.61 | 0.119 | −14.42 | 1.20 |
| 20 min | Test 1 | Reference | 9.47** | 0.001 | 3.44 | 15.50 |
| | Test 2 | Reference | 14.93*** | 0.000 | 8.90 | 20.96 |
| | Test 3 | Reference | 13.14*** | 0.000 | 7.11 | 19.17 |
| | Test 4 | Reference | 10.98*** | 0.000 | 4.95 | 17.01 |
| | Test 5 | Reference | −5.61 | 0.075 | −11.64 | 0.42 |
| 30 min | Test 1 | Reference | 6.89*** | 0.000 | 3.36 | 10.41 |
| | Test 2 | Reference | 8.44*** | 0.000 | 4.92 | 11.96 |
| | Test 3 | Reference | 14.43*** | 0.000 | 10.91 | 17.95 |
| | Test 4 | Reference | 11.54*** | 0.000 | 8.02 | 15.06 |
| | Test 5 | Reference | 1.37 | 0.753 | −2.15 | 4.89 |
| 45 min | Test 1 | Reference | 5.22** | 0.001 | 1.83 | 8.61 |
| | Test 2 | Reference | 6.84*** | 0.000 | 3.45 | 10.23 |
| | Test 3 | Reference | 13.05*** | 0.000 | 9.66 | 16.44 |
| | Test 4 | Reference | 9.76*** | 0.000 | 6.37 | 13.15 |
| | Test 5 | Reference | 1.45 | 0.682 | −1.94 | 4.83 |

[a] Difference between percents dissolved of test products and reference product.
* $P < 0.05$.
** $P < 0.01$.
*** $P < 0.001$.

min (first contrast), 10 versus 15 min (second contrast), 15 versus 20 min (third contrast), 20 versus 30 min (fourth contrast), and 30 versus 45 min (fifth contrast). For test products 1, 3, and 4, the percents dissolved were found to be significantly different at the first four contrasts ($P < 0.05$), but not to be significantly different at the fifth contrast ($P > 0.05$). This result showed the dissolution process continuing up to 30 min and being completed after this time point for these test products. While test 2 showed a significant difference at the first three contrasts ($P < 0.05$), it showed non-significant differences at the fourth and fifth contrasts ($P > 0.05$), indicating that the dissolution was completed at 20 min and a plateau was reached, as also seen in Fig. 1. For reference and test 5, significant differences were found at all contrasts, indicating that the dissolution continued up to 45 min (Fig. 1). By the repeated contrasts analysis, it was possible to inspect the course of dissolution over time for each drug product and in this way the last time points for dissolution were determined.

According to the results of ANOVA-based methods, while the dissolution profiles had differing shapes, in terms of course of dissolution and percent dissolved, test 5 showed the least departure from the reference.

### 3.2. Model-dependent methods

Mathematical models have been used extensively for the parametric representation of dissolution data (Table 1). The standard models in the dissolution data analysis are the cubic root law (Hixson and Crowell, 1931), square root of time equation (Higuchi, 1963), and first-order exponential function (Gibaldi and Feldman, 1967). For the general case of tablets, however, the interaction of disintegration and dissolution is complex and requires models which are applicable for S-shaped dissolution profiles. Weibull distribution (Langenbucher, 1972) as well as the logistic model (Rawlings, 1988) are able to describe S-shaped/sigmoidal dissolution profiles.

After fitting these models to the individual unit dissolution data, the selection was based on the comparisons of the following features of the models: (1) higher determination coefficient, (2) smaller absolute difference between each fitted and actual percent dissolved, and (3) smaller residual mean square (Table 4). Considering these criteria, the logistic model was that which fit best to the dissolution data of reference and test products, while the second best was Weibull distribu-

Table 4
Parameters of the mathematical models and descriptive statistics of regression for the dissolution data[a]

| Model | Statistics | Reference | Test 1 | Test 2 | Test 3 | Test 4 | Test 5 |
|---|---|---|---|---|---|---|---|
| First-order | $r^2$ | 0.9304 | 0.9432 | 0.9084 | 0.9485 | 0.9310 | 0.9437 |
| | $k$ | $6.10\times10^{-2}$ | $7.62\times10^{-2}$ | $8.70\times10^{-2}$ | $8.05\times10^{-2}$ | $7.40\times10^{-2}$ | $5.44\times10^{-2}$ |
| | S.E. | $2.15\times10^{-3}$ | $2.49\times10^{-3}$ | $3.77\times10^{-3}$ | $2.72\times10^{-3}$ | $2.93\times10^{-3}$ | $1.82\times10^{-3}$ |
| | $R_{max}$ | 12.38 | 10.76 | 15.95 | 11.83 | 11.96 | 13.01 |
| | RMS | 36.04 | 29.83 | 51.65 | 35.42 | 49.82 | 36.14 |
| Hixson-Crowell | $r^2$ | 0.8864 | 0.9278 | 0.9090 | 0.9704 | 0.9481 | 0.9307 |
| | $k$ | $7.99\times10^{-2}$ | $9.96\times10^{-2}$ | $11.25\times10^{-2}$ | $10.36\times10^{-2}$ | $9.65\times10^{-2}$ | $7.13\times10^{-2}$ |
| | S.E. | $3.42\times10^{-3}$ | $3.35\times10^{-3}$ | $4.18\times10^{-3}$ | $2.37\times10^{-3}$ | $3.04\times10^{-3}$ | $2.50\times10^{-3}$ |
| | $R_{max}$ | 17.65 | 14.00 | 12.83 | 8.81 | 9.36 | 14.23 |
| | RMS | 56.69 | 32.98 | 45.50 | 18.82 | 34.04 | 43.19 |
| Higuchi | $r^2$ | 0.8271 | 0.7763 | 0.6791 | 0.8265 | 0.8113 | 0.8548 |
| | $K$ | 14.36 | 15.64 | 16.31 | 16.38 | 15.83 | 13.89 |
| | S.E. | 0.35 | 0.41 | 0.50 | 0.40 | 0.43 | 0.36 |
| | $R_{max}$ | 15.23 | 18.95 | 20.90 | 20.90 | 17.50 | 20.24 |
| | RMS | 92.94 | 122.99 | 186.77 | 186.77 | 137.52 | 94.81 |
| Weibull | $r^2$ | 0.9304 | 0.9483 | 0.9310 | 0.9831 | 0.9703 | 0.9518 |
| | $T_d$ | 16.41 | 13.06 | 11.43 | 12.49 | 13.34 | 18.02 |
| | S.E. | 0.61 | 0.41 | 0.40 | 0.21 | 0.31 | 0.56 |
| | $\beta$ | 0.99 | 1.13 | 1.34 | 1.39 | 1.45 | 1.15 |
| | S.E. | $6.73\times10^{-2}$ | $8.20\times10^{-2}$ | $12.21\times10^{-2}$ | $5.78\times10^{-2}$ | $8.56\times10^{-2}$ | $6.89\times10^{-2}$ |
| | $R_{max}$ | 12.14 | 12.26 | 10.90 | 7.05 | 8.66 | 11.50 |
| | RMS | 36.08 | 25.66 | 33.55 | 10.97 | 19.17 | 30.18 |
| Logistic | $r^2$ | 0.9631 | 0.9754 | 0.9596 | 0.9799 | 0.9784 | 0.9779 |
| | $\alpha$ | −3.77 | −3.96 | −4.32 | −4.69 | −4.98 | −4.49 |
| | S.E. | 0.26 | 0.25 | 0.51 | 0.41 | 0.43 | 0.30 |
| | $\beta$ | 1.58 | 1.79 | 2.04 | 2.11 | 2.17 | 1.78 |
| | S.E. | 0.10 | 0.10 | 0.23 | 0.17 | 0.18 | 0.12 |
| | $R_{max}$ | 9.08 | 8.52 | 8.16 | 9.53 | 7.55 | 7.80 |
| | RMS | 19.48 | 13.26 | 22.56 | 13.62 | 15.75 | 14.29 |

[a] $r^2$, determination coefficient; $R_{max}$, maximum residual in absolute size between fitted and actual percents dissolved; RMS, residual mean square; S.E., standard error of model parameters, $k$, $\alpha$, $\beta$, and $T_d$.

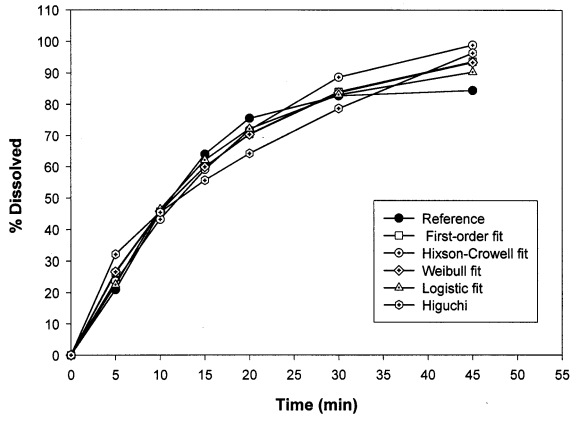


Fig. 2. Dissolution profiles generated from different model fits for reference product.

tion. Also the first-order model fit gave the statistical parameters as being approximately the same as those of Weibull distribution for the reference product, unlike other test products. As seen in Fig. 2, the profiles generated from logistic, Weibull, and first-order fits were closer to the reference profile than the profiles generated from Higuchi and Hixson Crowell fits. The fit of dissolution data to the logistic model and Weibull distribution emphasizes the S-shaped dissolution profiles of all drug products considered. The derived parameters of these models are given in Table 4. The model parameters were compared as test product against reference using $t$-test; the results are shown in Table 5. According to the logistic model, $\alpha$ (scale factor) and $\beta$ (shape factor) parameters of test products 1, 2, and 5 were found not to be significantly different from those of reference product, implying that the dissolution profiles of these test products were similar to the profile of reference. However, $T_d$ (time parameter) and $\beta$ (shape factor) parameters of Weibull distribution showed that only the dissolution profile of test 5 was similar to the reference profile. When these results are evaluated in the light of Fig. 1, Weibull distribution seems to be more precise than the logistic model for the discrimination of dissolution profiles; the profile of test 5 alone is close to the reference profile. This result was also in agreement with the result of ANOVA-based methods.

The preferred model was Weibull distribution with its parameters describing the types of dissolution profiles, and dissolution time. The shape parameter, $\beta$, characterizes the profile as either exponential ($\beta = 1$), S-shaped with upward curvature followed by a turning point ($\beta > 1$), or as one with steeper initial slope than consistent with the exponential ($\beta < 1$) (Langenbucher, 1972). $\beta$-Values greater than 1 for test products 2, 3, and 4 were significantly different from that of the reference ($P < 0.05$) indicating that their dissolution profiles are more pronounced sigmoidal shapes (Tables 4 and 5, Fig. 1).

Table 5
Comparisons of the derived model parameters of test products against reference product by $t$-test (two-sided) ($n = 36$)

| Product | | Difference, logistic $\alpha$ | $t$ | Difference, logistic $\beta$ | $t$ |
|---|---|---|---|---|---|
| Test 1 | Reference | −0.18 | 0.51 | 0.21 | 1.44 |
| Test 2 | Reference | −0.55 | 0.97 | 0.46 | 1.85 |
| Test 3 | Reference | −0.92 | 1.89 | 0.54* | 2.66 |
| Test 4 | Reference | −1.21* | 2.41 | 0.59* | 2.89 |
| Test 5 | Reference | −0.72 | 1.80 | 0.20 | 1.29 |
| | | Weibull $T_d$ | | Weibull $\beta$ | |
| Test 1 | Reference | −3.36* | 4.59 | 0.143 | 1.35 |
| Test 2 | Reference | −4.99* | 6.87 | 0.351* | 2.52 |
| Test 3 | Reference | −3.92* | 6.10 | 0.402* | 4.53 |
| Test 4 | Reference | −3.07* | 4.53 | 0.464* | 4.26 |
| Test 5 | Reference | 1.60 | 1.95 | 0.163 | 1.69 |

* $P < 0.05$.

Table 6
Difference factors ($f_1$) for reference versus test products

| Last point for dissolution (min) | $f_1$-Values | | | | |
|---|---|---|---|---|---|
| | Test 1 | Test 2 | Test 3 | Test 4 | Test 5 |
| 20 | 13.29 | 21.74 | 14.32 | 9.31 | 10.35 |
| 30 | 11.54 | 17.99 | 14.45 | 10.03 | 7.97 |
| 45 | 10.11 | 15.47 | 14.15 | 9.98 | 6.50 |

The time parameter, $T_d$, represents the time interval necessary to dissolve 63.2% of the drug substance (Langenbucher, 1972). The differences between $T_d$ values of tests 1–4 and the reference were found to be significant ($P < 0.05$) (Table 5). The time necessary to dissolve 63.2% of drug substance from these test products was shorter than that of reference (Table 4).

### 3.3. Model-independent methods

The $f_1$ (difference factor) is proportional to the average difference between the two profiles, whereas $f_2$ (similarity factor) is inversely proportional to the average squared difference between the two profiles, with emphasis on the larger difference among all the time points. The use of these factors was also recommended for dissolution profile comparison in the FDA's guides for industry (FDA, 1995, 1997a,b). According to these guides, generally, $f_1$ values up to 15 (0–15) and $f_2$ values greater than 50 (50–100) ensure sameness or equivalence of the two curves.

The values of $f_1$ and $f_2$ factors for test products versus reference were calculated from the means of percent dissolved at each time point (Table 2) by using Eqs. (1) and (2) and listed in Tables 6 and 7. Shah et al. (1998) recommended that, because of the sensitivity of these factors to the measurements after 85% dissolution, the number of sample points be limited to not more than one, once any of the product reaches 85% dissolution. For that reason, the values of factors $f_1$ and $f_2$ were calculated separately for the dissolution up to 20 min (the time at which 85% of drug substance is dissolved from any tested drug product), 30 min (the time at which the dissolution profiles nearly reach the final plateau), and 45 min (the time at which the dissolution process is completed).

As seen in Tables 6 and 7, $f_1$ and $f_2$ values for test products 1, 2, and 5 versus reference changed depending on the last point for dissolution considered. During the intervals 20, 30 and 45 min, $f_1$ values decreased while $f_2$ values increased. For test 2 versus reference, $f_1$ values were 21.7, 18.0 and 15.5 and $f_2$ values were 42.5, 44.0 and 45.4. As seen in Fig. 1, test 2 has the dissolution profile the furthest away from the profile of reference at the first 20 min, indicating a greater difference for dissolution up to this time point. When $f$-factors were calculated with the dissolution data up to 30 and 45 min, the difference decreased. For test 1 versus reference and test 5 versus reference, although the similarity degree changed in the same way, $f_1$ values were smaller than 15 and $f_2$ values were greater than 50, indicating that the dissolution profiles of test 1 and test 5 were similar to the profile of reference, unlike test 2.

For test 3 versus reference and test 4 versus reference, $f_2$ values depending on the last points for dissolution (20, 30 and 45 min) were inversely changed, implying decreased similarity between profiles (Table 7). This is because although the dissolution profiles of test 3 and test 4 were closer to the reference profile at the early time points, they did move away at the later time points (Fig. 1). Consequently, the dissolution profile of test 3 was found to be similar to that of reference for the dissolution up to 20 min ($f_2 = 51.3$), while it was found to be different for the dissolution up to 30 and 45 min ($f_2 = 48.7$ and 47.8, respectively). For test 4 versus reference, $f_2$ values showed the similarity of the dissolution profiles for each of

Table 7
Similarity factors ($f_2$) for reference versus test products

| Last point for dissolution (min) | $f_2$-Values | | | | |
|---|---|---|---|---|---|
| | Test 1 | Test 2 | Test 3 | Test 4 | Test 5 |
| 20 | 53.89 | 42.47 | 51.29 | 57.16 | 59.02 |
| 30 | 54.53 | 43.96 | 48.68 | 54.15 | 61.26 |
| 45 | 55.61 | 45.36 | 47.78 | 53.43 | 63.05 |

three last points for dissolution (Table 7), since the dissolution profile of test 4 was closer to the profile of reference than that of test 3 (Fig. 1). The change of $f_1$ values depending on the last point for dissolution was not so pronounced as that for $f_2$ values for test 3 versus reference and test 4 versus reference; the fact that $f_1$ values were smaller than 15 indicated that both test products had identical dissolution profiles to that of reference (Table 6). These results show that the similarity factor, $f_2$, is more sensitive for dissolution profile dissimilarity than the difference factor, $f_1$.

In conclusion, each method used here for the comparison of dissolution profiles seems to be applicable and useful. However, these methods gave different results regarding the similarity of dissolution profiles. In general, it was observed that ANOVA-based and model-dependent methods have narrower limits and are more discriminative than the $f$-factors. For application and interpretation $f$-factors are easier to use; only one value is obtained to describe the closeness of the two dissolution profiles. However, the last point for dissolution has to be determined in order to emphasize the difference between two profiles, since the values of the $f$-factors depend on this point. In the model-dependent methods, for the formation of a non-linear regression model, it is important that the assumption of least squares be continually checked (Rawlings, 1988). The application and evaluation of model-dependent methods are more complicated and these methods present an acceptable model approach to the true relationship between the dependent and independent variables. ANOVA-based methods including post hoc procedures provide a possibility for the comparison of dissolution data on the basis of point-by-point and for finding the sources of differences among the variables. It is possible to obtain detailed information about dissolution data which can be useful also in formulation development to match release of reference product. Consequently, ANOVA-based methods would seem to be more informative than the other comparison methods.

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