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An evaluation of fit factors and dissolution efficiency for the comparison of in vitro dissolution profiles

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Abstract

Dissolution efficiency (D.E.), the area under a dissolution curve between defined time points, and the fit factors (f_1 and f_2) have been compared for the characterisation of dissolution profiles, using data from three batches of a product in nine different packs stored under two conditions. The factors f_1 and f_2 offer ease of calculation and a simple measure of similarity between pairs of dissolution profiles. This is well suited to the qualitative determination of 'similarity' as required by the FDA's SUPAC Guide. However, they do not provide information on individual batches, including their consistency. In contrast, D.E. does provide such information and is well-suited to making quantitative comparisons amongst batches. Because D.E. has a simple physical meaning, it is easier to interpret D.E. data than corresponding f_1 and f_2 results. The confidence limits in D.E. values provide a useful measure of the variability in batch dissolution and allow the statistical significance of difference in D.E. between pairs of batches to be determined. Both the above measures lead to the same conclusions regarding the similarity in protective power amongst the nine packs under test and to the value of added desiccant in maintaining the dissolution profile of the product when stored under high humidity conditions. It is concluded that D.E. offers a suitable alternative to the single point dissolution measurement for QC of immediate release products.

Keywords: Dissolution profiles; Fit factors; Dissolution efficiency; Statistical equivalence; Bioequivalence

1. Introduction

During the recent past the purpose, design and interpretation of dissolution tests has received considerable attention [1–6]. In particular, the US Food and Drug Administration (FDA) Centre for Drug Evaluation and Research established working groups to consider the possibility of using in vitro dissolution data to demonstrate the bioequivalence of modified formulations or the same formulation following processing or site changes. The FDA has now published a guidance note for

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immediate release oral dosage forms [7], generally known as SUPAC (scale up and post approval changes), IR (immediate release). The equivalence of dissolution profiles is established using the fit factor, f_2 [8] , which is derived from comparing the % dissolution at a series of timepoints during dissolution.

During the course of development, in vitro dissolution results may be used as a guide to formulation optimisation and to compare different formulations. For both clinical and commercial batches of product, dissolution specifications are used for quality control purposes to demonstrate the consistency of product, its conformance with GMP and the absence of changes in dissolution behaviour during stability testing.

The widespread use of automated dissolution equipment means that dissolution curves are often generated for immediate-release products, where traditionally specifications were based on dissolution at a single time point, allowing the use of more sophisticated methods of comparing dissolution data amongst batches.

Polli et al. have compared a number of different approaches to comparing dissolution curves [2] using the example of different formulations of metoprolol tartrate. These included several model-independent approaches, namely, (a) ANOVA approaches, (b) the difference factor and the fit factors, f_1 and f_2 [8], and (c) the two indices (ς_1 and ς_2) of Rescigno [9]. In addition, eight model-dependent approaches were used including zero-order, first-order, Hixson-Crowell, Higuchi, quadratic and Weibull models. Whereas model-independent approaches make no assumptions regarding the shape of the dissolution curve, the model-dependant methods involve the use of defined equations in which parameters defining the curves shape are optimised. It was concluded that for the formulations studied the ANOVA approaches identified statistical, rather than pharmaceutical equivalence, where pharmaceutical equivalence means dissolution curves which are within typical dissolution specifications and statistical equivalence means not significantly different at the 95% confidence level.

The f_2 limit of 50 recommended by SUPAC IR [7] as a criterion of equivalence was regarded as conservative, because two formulations with $f_2 = 17.7$ were reported as bioequivalent ($f_2 = 100$ for identical dissolution profiles) [2]. Both the model-independent ratio test procedures and pair-wise procedures as well as three of the four model-independent procedures yielded numerical results which could serve as objective metrics for comparison of dissolution curves.

Tsong et al. [3] have used a statistical multivariate approach to the comparison of dissolution data. This includes determining if there is a statistical difference in the mean dissolution of test and reference products at a series of time points and assumes that both products meet certain statistical criteria (identical variance–covariance structure). The Mahalanobis distance (m-distance), D_m, was used to determine the overall statistical distance over all the timepoints between the two products.

Within Sanofi, it was decided to evaluate different methods of comparing dissolution profiles for immediate release products with a view to recommending preferred alternatives within the company. The evaluation is described in this paper.

1.1. Selection of models for evaluation

Some models result in the comparison between two dissolution curves being represented by a single number eg, f_2, ς_1, k (first order value constant) whereas most model-dependent approaches result in each curve being represented as two or more empirical parameters, such as, a, b and c from the Weibull equation:

$$\% \text{ dissolved} = a \cdot [1 - \exp(-(t/c)^b)]$$

It can be argued that where the shape of a dissolution curve is important it is necessary to describe the curve by at least two parameters—one (or more) describing the curve shape and one indicating the rate of dissolution. The fit factors could be used in this way if separate factors were calculated for early, middle and late parts of dissolution curves. For normal immediate release formulations we considered that a descriptor based on a single number is adequate.

During the course of formulation development it is important to measure intra-batch variation in dissolution as well as the mean, since the former

may indicate weaknesses in the manufacturing process. However, mean batch dissolution data are also of value in identifying critical manufacturing variables [4].

Models considered for examination by the authors, in addition to those evaluated by Polli et al., included mean dissolution time (MDT), mean residence time (MRT) [10] and dissolution efficiency (D.E.) [11,12], which are all related to the area under the dissolution curve. MDT and MRT are most applicable to controlled release products and were therefore not considered further. After some preliminary evaluation it was decided to compare D.E. and the fit factors f_1 and f_2 for a Sanofi tablet product in a range of packs affording different degrees of protection against moisture. More emphasis was placed on evaluating f_2 than f_1 because the former has been adopted for SUPAC.

2. Material and methods

2.1. Analytical methods

2.1.1. Experimental methods

For general dissolution parameters see USP⟨711⟩, apparatus II, rotating paddles. The automated system consisted of (1) apparatus 2 described in USP⟨711⟩, (2) a microprocessor with suitable program, (3) an eight port dissolution valve, (4) a peristaltic pump, (5) a suitable spectrophotometer equipped with a 1-cm flow cell, (6) a suitable recorder for the spectrophotometer readings, and (7) sampling probes.

All dissolution tests were conducted on a Hewlett Packard multi-bath dissolution testing system. The components are identified below:

CPU: HP Vectra Series 3.5/75 running MS-DOS™ 6.22, and Microsoft Windows™ Workgroups 3.11 Software. Application Software: HP 89551A multi-bath dissolution testing software revision 03.01 running in single bath mode. Spectrophotometer: HP 8452AX diode array spectrophotometer with multicell transport. HP IB and serial communications protocols. Sampling accessories: pump HP 89052B, 8-port valve HP 89079A, control (4 channel) HP 89078A. Dissolution bath: Distek model 2100A with thermostatic controller, TCS 0200.

2.1.2. Dissolution medium preparation

Dissolve 6.57 g of potassium chloride in 200 ml of water and add 119 ml of 0.1 N hydrochloric acid. Dilute with water to 900 ml and check the pH. If necessary, adjust the pH to 2.0 (± 0.05) with 0.1 N hydrochloric acid or 0.1 N sodium hydroxide. Dilute with water to 1000 ml and verify the pH. Deaerate the dissolution medium by a suitable means just prior to use. Scale up as necessary.

2.1.3. Bath preparation

Set the motor speed at 75 rpm and the constant temperature bath at 37°C. Place 1000 ml of dissolution medium in each of six vessels, which previously have been immersed in the constant temperature bath, and allow the medium to come to a temperature of 37 ± 0.5°C.

2.2. Statistical methods

2.2.1. Standardisation of data

If a measurement is performed at time 0 and if the value is slightly different from 0, then standardisation is necessary to give 0 dissolution at time 0. Measurements were not performed at time 0 in the dissolution studies evaluated in this paper. In order to calculate D.E. the curve of dissolution versus time was extrapolated to $t = 0$ using the equation used to model the curve.

The analysis assumes that 100% of product is dissolved at the last measured time, but, in practice, the last measurement is always different from 100. Sometimes, the difference is not very large and it can be explained by the error of the analysis system or by an error in the weight of the initial product. In these cases, it is better to standardise the data to give 100% dissolution of the last time point. This allows a comparison of the true dissolution curves rather than the uncertainty in the data.

If the last measurement is different from 100% because the product is not completely dissolved, the data must not be standardised. For the dissolution studies evaluated in this paper, standardisa-

tion of the last measurement time was not necessary.

2.2.2. Fit factors

Fit factors or similarity indices were introduced by Moore and Flanner [8] in 1996 and are defined as follows:

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

and

$$f_2 = 50 \log \left\{ \left[1 + \frac{1}{n} \Sigma\, w_t (R_t - T_t)^2 \right]^{-0.5} \times 100 \right\}$$

where R_t is the percentage of dissolved product for a reference batch at time point t, T_t is the percentage of dissolved product for the test batch, n is the number of time points and w_t an optional weight factor. The weight factor can be adjusted to give high or low weightings to selected time points as required. For example, if it is important to achieve a certain dissolution level by 40 min, the 40 min time point should be given a high weighting. The present study uses $w_t = 1$, meaning that each time point is weighted equally. For each batch, the calculations were made on the mean values for all the vessels.

The factor, f_1, is the average % difference over all time points in the amount of test batch dissolved as compared to the reference batch. The f_1 value is 0 when the test and the reference profiles are identical and increases proportionally with the dissimilarity between the two profiles.

The f_2 value is between 0 and 100. The value is 100 when the test and the reference profiles are identical and approaches zero as the dissimilarity increases, but because f_2 is a log function small differences in profile lead to a large drop in f_2.

Some authors recommend not including more than one time point after 80% because both f_1 and f_2 use data for all time points and the region of interest is normally between 0 and about 80% dissolution. The number of data from the plateau region of the dissolution curves, where differences between batches are at their smallest (zero if normalised to 100% at last time point), will influence the magnitude of f_1 and f_2. If there are only two data points after 80% dissolution, it is sensible to include both.

2.2.3. Dissolution efficiency

This concept was proposed by Khan and Rhodes in 1975 [11] and is defined as follows:

$$\text{Dissolution efficiency (D.E.)} = \frac{\int_{t_1}^{t_2} y \cdot \mathrm{d}t}{y_{100} \cdot (t_2 - t_1)} \times 100\%$$

where y is the percentage of dissolved product. D.E. is then the area under the dissolution curve between time points t_1 and t_2 expressed as a percentage of the curve at maximum dissolution, y_{100}, over the same time period. It is preferable to choose a time interval corresponding to 70–90% dissolution unless one wishes to compare an early part of the dissolution curve. Normally $t_1 = 0$ for a tablet where there is no lag phase. For a capsule product, t_1 can be set to the period corresponding to disintegration of the capsule shell. In the current study $t_1 = 0$ and $t_2 = 30$ min.

The main difficulty is to calculate the integral of the numerator, i.e. the area under the curve. There are two possibilities: a model independent method or a model dependent method.

(i) The model independent method

A well known method is the trapezoidal one. The area under the curve is the sum of all the trapeziums defined by:

$$\text{AUC} = \sum_{i=1}^{i=n} \frac{(t_1 - t_{i-1})(y_{i-1} + y_i)}{2}$$

where t_i is the ith time point, y_i is the percentage of dissolved product at time t_i.

A preferred alternative is the Simpson method [13]:

Three consecutive points are connected using a parabolic function. The area under this second order polynomial is then calculated by integration. This is done on all the measured points.

(ii) Model dependent methods

The aim here is to find a model which fits the data well.

Three non-linear models were evaluated in this study: the Weibull, the Logistic and the Gompertz models. Their equations are:

Table 1
f_1 values for each batch in both storage conditions

	25°C/60% RH			40°C/75% RH		
	Batch 1	Batch 2	Batch 3	Batch 1	Batch 2	Batch 3
CB/OB	12	5	2	14	12	18
CB/FB	6	4	2	66	53	26
OB/FB	5	2	4	47	73	53
B-7/B-7D	2	8	3	14	28	9
B-90/B90D	4	4	1	2	12	8
B-500/B-500D	2	3	5	4	1	13

Table 2
f_2 values for each batch in both storage conditions

	25°C/60% RH			40°C/75% RH		
	Batch 1	Batch 2	Batch 3	Batch 1	Batch 2	Batch 3
CB/OB	73	63	79	58	59	**48**
CB/FB	59	68	82	**24**	**27**	**38**
OB/FB	65	87	69	**28**	**23**	**28**
B-7/B-7D	79	58	78	**46**	**34**	53
B-90/B-90D	73	68	97	83	51	56
B-500/B-500D	79	73	66	70	95	**48**

Table 3
f_2 values for each batch and each pack comparing 25°C/RH with 40°C/75% RH

	CB	OB	FB	B-7	B-7D	B-90	B-90D	B-500	B-500D
B1	**22**	**25**	52	**43**	78	54	58	**47**	**44**
B2	**22**	**21**	64	**43**	77	54	72	**49**	**45**
B3	**28**	**21**	52	58	91	**40**	54	73	**37**

Weibull: $\%\ \text{dissolved} = a \cdot [1 - \exp(-(t/c)^b)]$

Logistic:

$\%\ \text{dissolved} = a + c/(1 + \exp(-b(t-d))$

Gompertz:

$\%\ \text{dissolved} = a \cdot \exp(-\exp(-b - ct)) - d$

The Weibull model has three unknown parameters and the Logistic and Gompertz models have four unknown parameters. Therefore, an absolute minimum of five measured points are needed to fit these models. The best fit was obtained using non linear regression with the least square (LS) method and the function then numerically integrated over the chosen time period. The calculations were made for each individual vessel. Thus one can obtain the D.E. mean for each batch (6 vessels) with its standard error. One can compare D.E. means and their standard error or confidence intervals amongst batches. One can also measure the difference between the D.E. of the reference batch and the test batch.

If the difference and the 95% confidence interval of difference are within appropriate limits ($\pm$ 10% for example), one can conclude that the reference and test dissolution profiles are equivalent.

Table 4
f_2 values comparing for each batch the foil blister pack (FB) with other packs at 40°C/75% RH

	FB/CB	FB/OB	FB/B-7	FB/B-7D	FB/B-90	FB/B-90D	FB/B-500	FB/B-500D
B1	**24**	61	90	65	90	80	72	61
B2	**27**	**23**	**42**	58	57	78	60	63
B3	**38**	**28**	93	51	69	70	67	56

3. Results

3.1. Plan of data analysis

A Sanofi tablet product was used to compare two methods: The f_2 (and f_1) similarity factors and dissolution efficiency (D.E.).

The data set comprised the % of dissolved active for tablets from three batches (B1, B2, B3) stored at different temperature/humidity conditions (25°C/60% RH and 40°C/75% RH, respectively) in nine different packages:

Pack number	Description
CB	Clear blister
OB	Opaque blister
FB	Foil blister
B-7	7-count HDPE bottle
B-7D	7-count HDPE bottle with desiccant
B-90	90-count HPDE bottle
B-90D	90-count HPDE bottle with desiccant
B-500	500-count HPDE bottle
B-500D	500-count HPDE bottle with desiccant

The measurements were made at 5, 10, 15, 20, 25 and 30 min. For each data set (storage condition × package × batch) dissolution assays were performed using six vessels.

All the following calculations were made over 30 min. The D.E. calculations were made after fitting the data with the Weibull function (Weibull was chosen from the three models considered because it gave the best fit for the data).

3.2. Analysis of data using f_1 and f_2

For each storage condition and each batch, selected inter-pack comparisons were made. For f_1, this was limited to comparison between the three blister packs (Table 1) and between pairs of bottles with and without desiccant. For f_2 the same comparisons were made as for f_1 (Table 2). Since the results showed some packs did not afford good protection at 40°C/75% RH a direct comparison was then made to determine the effect

Table 5
Mean dissolution efficiencies with 95% confidence intervals

Pack	25°C/60% RH			40°C/75% RH		
	Batch 1	Batch 2	Batch 3	Batch 1	Batch 2	Batch 3
FB	79 (77,81)	76 (71,80)	75 (69,80)	73 (68,78)	72 (66,78)	67 (64,70)
CB	74 (67,81)	79 (76,83)	77 (74,79)	42 (34,51)	46 (40,51)	52 (46,59)
OB	76 (73,80)	75 (67,82)	78 (74,82)	49 (44,53)	40 (36,45)	43 (40,59)
B-7	76 (72,80)	70 (68,73)	74 (70,77)	66 (61,71)	59 (52,67)	68 (64,72)
B-7D	74 (68,80)	76 (72,80)	75 (71,78)	76 (70,82)	78 (75,81)	75 (70,80)
B-90	78 (73,82)	73 (69,76)	78 (74,81)	72 (69,75)	65 (57,74)	64 (55,73)
B-90D	75 (71,83)	76 (73,78)	78 (72,83)	71 (66,77)	74 (70,79)	70 (66,75)
B-500	78 (74,83)	75 (70,81)	73 (70,77)	70 (67,73)	67 (61,72)	71 (66,76)
B-500D	77 (75,79)	77 (74,81)	77 (75,80)	68 (63,73)	67 (61,74)	61 (53,70)

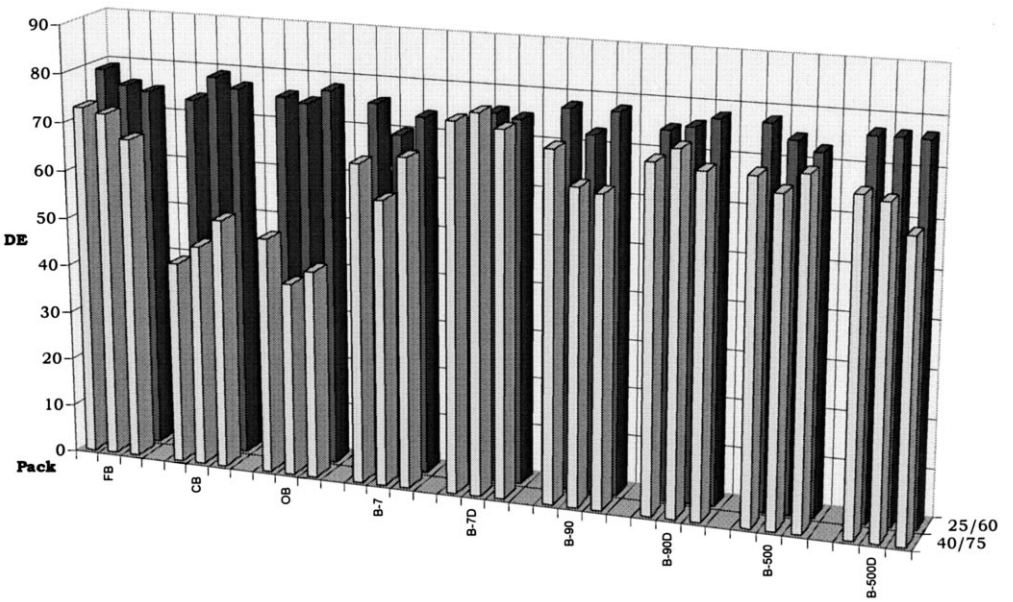

Fig. 1. D.E. for each batch and each pack at 25°C/60% RH and 40°C/75% RH.

of storage condition (25°C/60% RH and 40°C/75% RH) with each pack conditions (Table 3). Finally, it was thought useful to compare a highly protective pack (foil blister) with all the other packs at 40°C/75% RH (Table 4).

3.3. Analysis of data using D.E.

Dissolution efficiency data with the 95% confidence intervals (CI) are presented in Table 5. These data are shown in Fig. 1. It can be seen that the range of D.E. at 25°C/60% RH is from 70–79, i.e. a narrow range, and the CIs are consistent across batches and packs. However, at 40°C/75% RH, D.E. ranged from 40–78 and CIs were relatively large (>6) in a few cases; D.E. was generally lower than at 25°C/60% RH. In comparing D.E. data we used differences rather than ratios, because it is too complicated to calculate the CI of a ratio. Results were analysed using the same comparisons as selected for f_2 and results are presented in Tables 6–8.

Table 6
95% Confidence intervals for the difference in D.E. between packages

Comparison	25°C/60% RH			40°C/75% RH		
	Batch 1	Batch 2	Batch 3	Batch 1	Batch 2	Batch 3
CB/OB	−2 (−8,3)	5 (−1,10)	−1 (−5,2)	−6 (−13,1)	5 (0,10)	10 (0,14)
CB/FB	−5 (−9,0)	4 (0,7)	2 (−2,6)	−31 (−37,−24)	−27 (−32,−21)	−15 (−20,−10)
OB/FB	−2 (−5,1)	−1 (−7,5)	3 (−1,8)	−25 (−29,−20)	−32 (−37,−26)	−24 (−27,−22)
B-7/B-7D	2 (−3,7)	−6 (−9,−3)	−1 (−4,3)	−10 (−16,−5)	−18 (−24,−13)	−7 (11,−3)
B-90/B-90D	3 (−1,7)	−3 (0,−6)	0 (−5,4)	1 (−3,5)	−9 (−16,−2)	−7 (−14,0)
B-500/B-500D	1 (−2,5)	−2 (−6,−3)	−4 (−7,−1)	2 (−2,6)	−1 (−6,5)	10 (−17,3)

Table 7
D.E. differences and 95% confidence intervals for each batch in blister packs comparing 25°C/60% RH with 40°C/75% RH

	CB	OB	FB
B1	−33 (−42,−24)	−28 (−33,−23)	−7 (−12,2)
B2	−33 (−38,−27)	−34 (−41,−28)	−4 (−10,3)
B3	−24 (−30,−18)	−36 (−39,−32)	−9 (−13,−5)

4. Discussion

4.1. Comparisons amongst blister packs

4.1.1. Results using f_1 and f_2

The three packages were compared with each other (Tables 1 and 2). For the 25°C/60% RH condition all the (f_2) values were above 50 and therefore one would conclude that the dissolution profiles were similar, independent of batch and the type of package. The conclusion was the same with the f_1 results: all the f_1 values were ≤ 12. The dissolution profiles shown in Fig. 2 illustrate the point.

For the 40°C/75% RH condition the f_2 values for clear versus opaque blister packages were above 50 for batches B1 and B2 and near 50 for batch B3, so the packages were equivalent under these conditions. Values below 50, which indicate potential inequivalence (average difference of 10%) according to SUPAC [7] are shown in bold. However, the f_2 values (Table 2) for the foil blister package relative to the clear and opaque blisters showed a difference in dissolution profile (Fig. 3), due to a reduction in dissolution rates with clear and opaque blisters (see Table 5 for dissolution efficiencies). The same conclusion can be drawn using f_1 values (Table 1), where the corresponding f_1 values are high (26–66).

Table 3 shows the f_2 values for the comparison of each pack at the two different storage conditions. The relative insensitivity of the foil blister pack to storage condition is shown by the high f_2 values (52–64). The corresponding D.E. data in Table 7 show a reduction in D.E. of between 4–9%.

The foil blister was therefore selected as the reference pack for comparison with all the other packs at 40°C/75% RH (Table 4). The f_2 figures show a fairly consistent pattern across the three batches in the comparison with the clear blister, but less so in the case of the opaque blister.

4.1.2. Results of the D.E. analysis

Comparing results amongst blister packs and batches at 25°C/60% RH (Table 6) all are equivalent, in agreement with the results obtained with f_2 (Table 2). In all cases where $f_2 < 40$, the $\Delta D.E.$ value was equal to or greater than 10. However, the f_2 value of 48 (CB/OB, batch 3 40°C/75%RH) corresponded to a difference in D.E. of 10. This is a small difference, which is not statistically significant whereas an f_2 value < 50 is taken to indicate a potential difference in in vivo dissolution). Therefore, a decision based on an f_2 value is not supported by the D.E. result. However, a comparison of the two dissolution curves (Fig. 4) shows that dissolution is incomplete at 30 min, with the product in the OB pack dissolving more slowly. Using the graph alone, without the confidence intervals, one might well conclude that there was a true difference.

Table 7 shows a large reduction (24–36%) in D.E. for the clear and opaque blister packs in changing from the 25°C/60% RH condition to 40°C/75% RH. A consistent pattern is seen across all three batches. These data are easier to interpret than the corresponding f_2 data in Table 3. The superiority of the foil pack is very clear.

4.2. Comparison of bottles

4.2.1. Results using f_1 and f_2

Pairs of bottles with and without desiccant were used. Under normal storage conditions (25°C/60% RH), the desiccant had no effect, with f_1 covering the range 1–8 and f_2 the range 58–97 (Tables 1 and 2). However, at 40°C/75% RH, f_2 was lower for the 7-count bottles (34–53) and variable for the 90-count and 500-count bottles (48–95 and 51–83, respectively). One would conclude that the desiccant is most effective in the 7-count bottle. This may be related to the fact that this pack is more sensitive to storage conditions than the higher-count bottles and the desiccant to content ratio is at a maximum in the smaller pack. Using

Table 8
D.E. differences and 95% confdence intervals for each batch in bottle comparing 25°C/60% RH with 40°C/75% RH

	B-7	B-7D	B-90	B-90D	B-500	B-500D
B1	−14 (−19,−8)	−1 (−7,6)	−8 (−12,−4)	−7 (−13,−1)	−11 (−16,−7)	−11 (−16,−7)
B2	−17 (−24,−9)	−1 (−4,2)	−10 (−19,−2)	−4 (−8,1)	−10 (−16,−3)	−12 (−18,−5)
B3	−7 (−12,−3)	−1 (−5,3)	−13 (−22,−4)	−7 (−13,−1)	−5 (−10,1)	−17 (−26,−9)

the f_2 comparison alone it is not easy to draw further conclusions. Figs. 5 and 6 giving the dissolution curves at 40°C/75% RH for the 7-count and 500-count bottles with and without desiccant and clearly illustrate the point. Comparison of f_1 and f_2 show the expected inverse relationship.

Comparing the effect of storage condition on bottles with and without desiccant, Table 3 shows more clearly than Table 2 that the addition of desiccant to the 500-count bottle had little effect in preventing the retardation of dissolution rates in the 40°C/75% RH condition. Desiccant was of some benefit in the 90-count bottle. However, it is easier to interpret these effects by referring to the difference in D.E. values (Table 8), the result of which are discussed below.

Comparing the foil blister with the six bottle packs at 40°C/75% RH (Table 4) shows that all are equivalent, with an f_2 range of 51–90, except for batch 2, where $f_2 = 42$ for the 7-count bottle. This reflects the slow dissolution of the product in this pack.

4.2.2. Results using D.E.

The results at 25/60 support the conclusions drawn from the f_2 analysis. There is fairly close correlation (Spearman's rho $= -0.936$) between f_2 and the $\Delta D.E.$ values, ignoring the $\pm$ sign, for comparisons between pairs of packs at 40°C/75% RH, as shown in Fig. 7, with a non-linear relationship. Because of the large uncertainty in the lower values of $\Delta D.E.$ some scatter is to be expected.

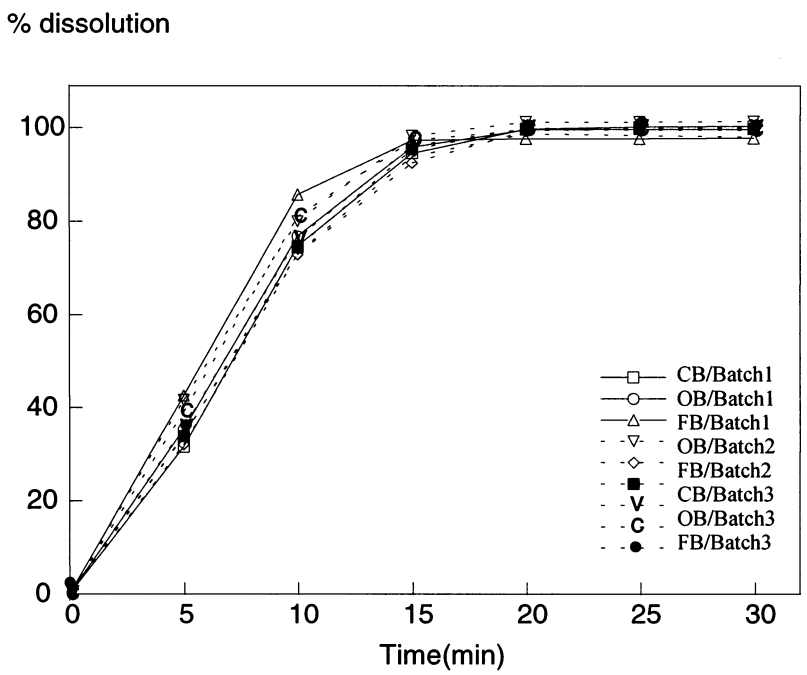

Fig. 2. Mean dissolution curves for blister pack and each batch at 25°C/60% RH.

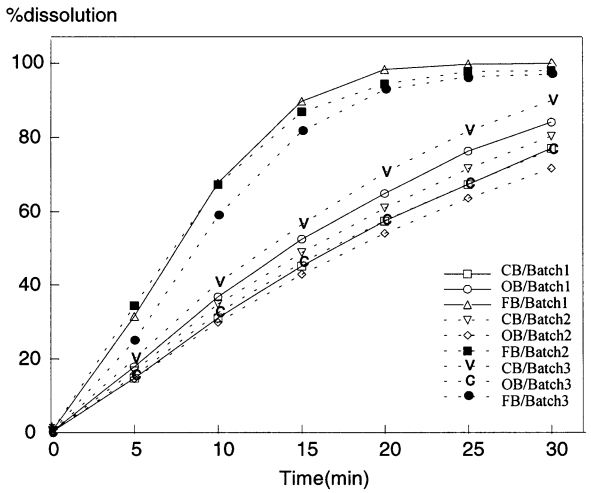

Fig. 3. Mean dissolution curves for blister packs and each batch at 40°C/75% RH.

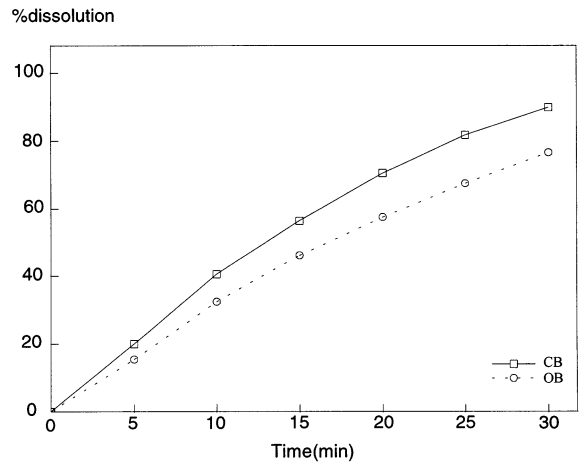

Fig. 4. Dissolution curves for OB and CB packs at 40°C/75% RH batch 3 ($f_2 = 48$, $\Delta D.E. = 10$).

The data in Table 8 shows that the reduction in D.E. between the two conditions is fairly consistent for five of the six bottles, ranging from 4–17%. The addition of desiccant had a marked effect on the 7-count bottle, where the reduction in D.E. was only 1%, whereas with the higher count bottles, the D.E. change was essentially unaffected; possibly insufficient desiccant was added.

4.3. Comparison between similarity indices and D.E.

The calculation of the f_1 and f_2 is very simple but the analyses must be made with the same time points. In the comparison of two batches, the intra-batch variability is hidden because the calculations need to be made on the mean. In addition, to use f_1 and f_2 one must define a reference batch

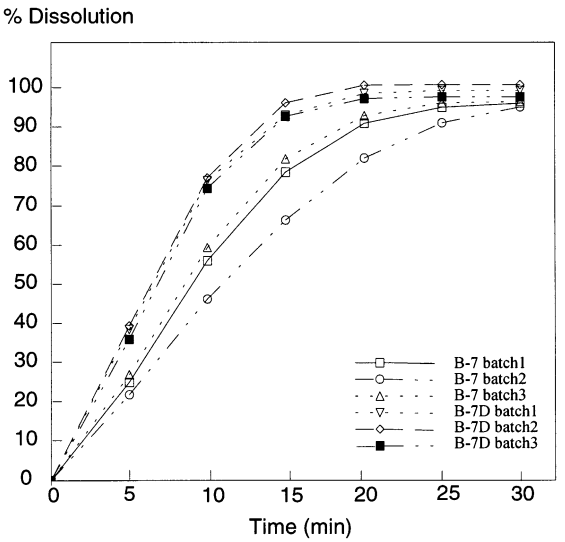

Fig. 5. Dissolution curves for 7-count bottles with and without dessicant at 40°C/75% RH.

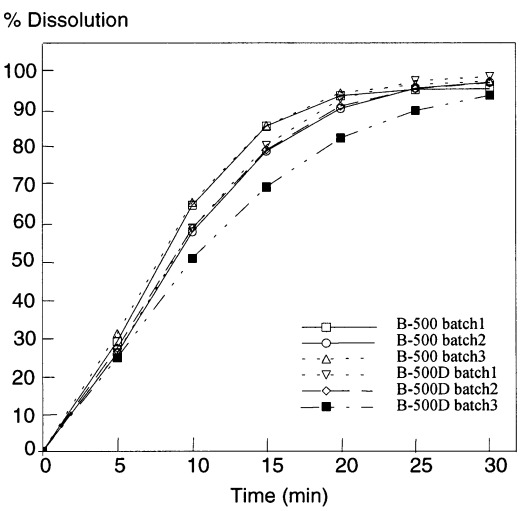

Fig. 6. Dissolution curves for 500-count bottles with and without dessicant at 40°C/75% RH.

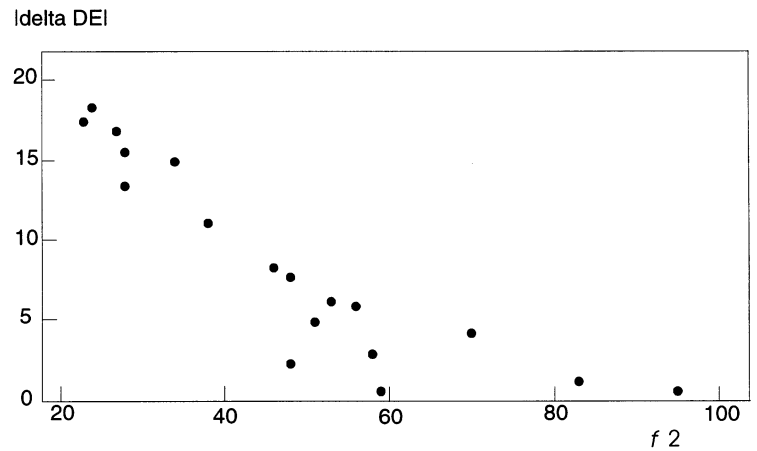

Fig. 7. Relationship between f_2 and $\Delta D.E.$ for comparisons between pairs of packs at 40°C/75% RH.

and for f_1 the conclusions depend on the batch chosen for reference.

The f_2 value does not change proportionally with the dissimilarity between two profiles. It is more sensitive when the difference between the two profiles is small. The FDA recommended this method for SUPAC [7] and suggested 50 as a threshold value. It is well suited to use in this mode to decide between similarity/dissimilarity of profiles. However, even though f_2 is quite closely correlated with $\Delta D.E.$ it is more difficult to interpret f_2 than D.E. data without reference to dissolution data or curves, since it relates to differences between curves, and because of its non-linear behaviour. The f_1 value increases proportionally with the dissimilarity between two profiles, with a maximum value of 100%. A value of 10 corresponds to an f_2 value of approximately 50.

The calculation for the D.E. is more complex than that for f_2. Some authors have proposed the linearisation of the Weibull function and weighted linear fitting [14]. Nowadays, fitting non-linear models is easily programmed and the calculations are rapid. The area under the curve is then determined by numerical integration. To choose the best fit model, it can be useful to have a criterion of goodness of fit in addition to inspecting the graphs. As the models do not have the same number of parameters the value of R^2 Adjusted seems to be a good criterion to compare models. If no model fits well, it is better to use the model independent method. The trapezium lacks accuracy and it is preferable to use the Simpson method for the integration.

Using D.E. allows comparisons amongst batches when D.E. has been calculated using different models, although, in this case it is impossible to compare the model parameters. All these methods can be applied using any period of time.

The main advantage of using D.E. is that no reference batch is needed and the result is closely related to dissolution behaviour. In addition, the graphical representation of D.E. $\pm$ standard deviation readily allows quality control by checking for drift in mean and dispersion of dissolution curves (c.f. statistical process control). An equivalence approach is also possible with this method: the main difficulty is to define the equivalence bounds. These bounds have to be defined by the knowledge of the product and the inter-batch differences: in the literature, bounds of 10% are often used. Finally, the D.E. method permits the evaluation of the intra-batch variability.

A formal comparison between D.E. and the commonly used single point dissolution result (mean % dissolved at a selected time) has not been made in this work, but it is clear that the information content of D.E is different in that it gives a measure of the dissolution behaviour of the batch in question relative to a 'perfect' batch which dissolves instantaneously. As recognised by the FDA's SUPAC Guideline, a comparison which

takes the whole of the dissolution process into account is preferable over one which is a measure at a single time point, even for 'immediate' release products.

5. Conclusions

The similarity indices and the D.E. methods are two different methods of analysing dissolution profiles and may be applied in different situations. The fit factors f_1 and f_2 are useful when the aim is to compare two formulations in order to demonstrate bioequivalence, however, sufficient pairs of batches should be compared to obtain a statistically significant result. Pairs of batches can also be compared using D.E. and equivalent conclusions drawn. Where a quantitative comparison is required D.E. is a more suitable parameter and when limits are set on D.E. it can be used for quality control in place of the conventional dissolution level. Additionally, the variability (95% CIs) in D.E. is a useful measurement of batch homogeneity with respect to dissolution and this too can be used to monitor the homogeneity of batches.

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References

[1] FIP Guideline, Drug Inform. J. 30 (1996) 1071–1084
[2] J.E. Polli, G. Sing Rekhi, V.P. Shah, Drug Inform. J. 30 (1996) 1113–1120.
[3] Y. Tsong, T. Hammerstrøm, P. Sathe, V.P. Shah, Drug Inform. J. 30 (1996) 1105–1112.
[4] L.T. Grady, Drug Inform. J. 30 (1996) 1063–1070.
[5] D.E. Storey, Drug Inform. J. 30 (1996) 1039–1044.
[6] D.L. Simmons, A.A. Legore, P. Picotte, N.N. Joshi, J. Pharmacokin, Biopharma 3 (1975) 39–49.
[7] Food and Drug Administration, Federal Register, Part IV, 60 (230) (1995) 61638–61643.
[8] J.W. Moore, H.H. Flanner, Pharm. Technol. 6 (1996) 64–74.
[9] A. Rescigno, Pharm. Res. 9 (7) (1992) 925–928.
[10] F. Podczeck, Int. J. Pharm. 97 (1993) 93–100.
[11] K.A. Khan, C.T. Rhodes, Pharm. Acta Helv. 47 (1972) 594–607.
[12] K.A. Khan, Communications, J. Pharm. Pharmacol. 27 (1975) 48–49.
[13] J.-H. Cohen, F. Joutel, Y. Cordier, B. Jech, Turbo Pascal: Initiation et Applications Scientifiques, Ellipses, Paris, 1989.
[14] F. Langenbucher, Pharm. Ind. 38 (5) (1976) 472–477.