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# Evaluation of dissolution profiles using principal component analysis

E. Adams [a,*], R. De Maesschalck [a], B. De Spiegeleer [b], Y. Vander Heyden [a], J. Smeyers-Verbeke [a], D.L. Massart [a]

[a] *Vrije Universiteit Brussel, Pharmaceutical Institute, Laarbeeklaan 103, B-1090 Brussels, Belgium*
[b] *Health Engineering and Assurance, Keizer Karelstraat 228, B-9000 Gent, Belgium*

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**Abstract**

The performance of principal component analysis (PCA) for the evaluation of dissolution profiles is examined and compared with other methods such as the similarity factor and the calculation of the area under the curve. Both simulated and real data from the pharmaceutical industry are used. The PCA scores plots of the dissolution curves provide information about the between- and within-batch variations. Differences in level or shape can be observed in the first two principal components (PCs). Irrelevant irregularities, which have a strong influence on the similarity factor, are neglected in PC1/PC2. To detect outliers in a set of dissolution curves, PCA was preferred above Hotelling's $T^2$ test. In general, PCA is found to be a useful technique to examine dissolution data visually, but however, it does not contain criteria to decide if batches are similar or not. This can be done by combining PCA with the resampling with replacement or bootstrap method to construct confidence limits. 

*Keywords:* Dissolution; Chemometrics; Similarity factor $f_2$; Principal component analysis

## 1. Introduction

The evaluation of dissolution profiles is a very important quality measure for solid oral drug delivery systems (tablets and capsules). It is used during the development of the galenic formulation, as quality control during the production, for evaluating the stability of the tablets or the capsules and as an evaluation for comparing new or generic formulations with an existing one. It can also provide a basis for achieving an in vivo–in vitro correlation. The Food and Drug Administration (FDA) allows the use of only in vitro dissolution testing to ensure the product quality in case of certain scale-up and post approval changes (SUPAC) like manufacturing site changes, increase or decrease of batch size and small quantitative changes in excipients (FDA Guidance for Industry, 1995, 1997). For most dissolution tests, the dissolution characteristics of

* Corresponding author. Tel.: +32-247-74723; fax: +32-247-74735.
*E-mail address:* eadams@fabi.vub.ac.be (E. Adams).

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the test batch have to be compared with those of the reference batch. The simplest way to do this is by checking whether after a certain time a minimum percentage of the active is dissolved in the dissolution medium. Although the use of this single-point dissolution test may be sufficient for highly soluble and rapidly dissolving drug products, the FDA recommends measurements at more time points, especially in the case of slowly dissolving or poorly water-soluble drugs. Dissolution curves with an equal dissolution after the predetermined time can have a different shape before reaching that time point, which, from a pharmacokinetic point of view, can lead to different plasma concentration profiles in the patient.

From a computational point of view, it is more complex to compare multiple time points or complete dissolution profiles than a single-point test. In the literature different methods are described for comparing dissolution profiles. Polli et al. (1997) divided them into ANOVA-based, model-independent and model-dependent techniques. Depending on the method used for the comparison, different results can be obtained.

The ANOVA-based methods, which can also be regarded as model independent, test the dissolution profiles for differences in level and shape (Mauger et al., 1986). These methods were found to be overly discriminating ($P$ values $< 0.0002$) and investigated statistical rather than pharmaceutical equivalence (Polli et al., 1996). The difference factor $f_1$ and similarity factor $f_2$ were introduced by Moore and Flanner (1996) and discussed further in other papers (Polli et al., 1996; Shah et al., 1998; Anderson et al., 1998; O'Hara et al., 1998). Both the factors are recommended by the FDA for comparison of dissolution profiles of solid oral dosage forms, but the $f_2$ factor is preferred (FDA Guidance for Industry, 1995, 1997). Values of $f_1$ between 0 and 15 and of $f_2$ between 50 and 100 indicate equivalent dissolution profiles. The indices of Rescigno (1992) are closely related to the fit factors of Moore and Flanner. Tsong et al. (1996) applied a multivariate approach, namely the Mahalanobis distance (MD) computed between the mean of the reference batch and the mean of the new batch using the pooled variance–covariance matrix. The MD as a distance measure has the advantage over the Euclidean distance (ED) in that the correlation between the time points is taken into account. The test as proposed by Tsong et al. however has the disadvantage that the pooled variance–covariance matrix is used. This means that it is assumed that the variance–covariance matrices of both batches are the same, which in practice is often not the case. Another way of evaluating dissolution curves is to compare their dissolution efficiencies (DE) (Anderson et al., 1998). In fact, this method calculates and compares the areas under the curve (AUC). Depending on the way of computing the AUC, the method can be regarded as model dependent or independent.

In the model-dependent techniques, the measured points of the dissolution curve are fitted to functions like the Weibull, logistic, Gompertz, quadratic, Hixson–Crowell or Higuchi. To determine the parameters, non-linear regression (NLR) can be used. Polli et al. (1997) compared different fit functions and stated that the suitability of the functions strongly depends on the shape of the dissolution profiles and that not one model can be suggested for all types of dissolution curves. The model used for the test set may even not be the same as that for the reference set. The Weibull function seems to be one of the better methods to fit the different types of dissolution profiles.

In this paper we evaluate the use of PCA (Vandeginste et al., 1998) for exploring the data. The results of this method and the similarity factor $f_2$ are compared for both simulated and real data.

## 2. Methods

### 2.1. The similarity factor

The similarity factor $f_2$ introduced by Moore and Flanner (1996) can be computed as:

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

with $R_t$ and $T_t$ being the percentages of active dissolved at time $t$ (for $t = 1, 2, \ldots, n$) for, respec-

tively, the reference and the test or new formulation. The measurements at each time can be weighted according to their importance in the dissolution curve using the optional weight factor $w_t$. Usually each time point is weighted equally ($w_t = 1$). The new and the reference formulation are considered to be equal when $f_2$ is higher than 50. This value was determined empirically by considering that there may be no more than a 10% average difference at any sample time point. It is also recommended not to include measurement times at which the dissolution curves have a dissolution higher than 85% since the number of such sample points influences $f_2$ (Shah et al., 1998). The advantage of the $f_2$ factor is that it is easy to compute. However, this factor does not take into account the within-batch variability or the correlation between the data.

### 2.2. Principal component analysis

Principal component analysis (PCA) is a technique that provides a way to explore multivariate data. Many algorithms are described to perform PCA. In this article, the singular value decomposition (SVD) is used on $\mathbf{X}_c$, the column centred matrix of $\mathbf{X}$:

$$\mathbf{X}_c(m \times p) = \mathbf{X} - \bar{\mathbf{X}} = \mathbf{U}(m \times a)\mathbf{\Lambda}(a \times a)\mathbf{V}^T(a \times p) = \mathbf{T}(m \times a)\mathbf{V}^T(a \times p) \quad (2)$$

with $m$ being the number of objects (here, the number of tablets measured in the batch), $p$ the number of original variables (here, the number of time points) and a the number of principal components (PCs), with $a = m - 1$ if $m \leq p$ or $a = p$ if $m > p$. $\mathbf{U}$ is the unweighted (normalised) score matrix and $\mathbf{T}$ is the $(m \times a)$ weighted (unnormalised) score matrix with the PCs in the columns. $\mathbf{V}$ is the $(p \times a)$ loading matrix with $a$ column vectors, the so-called eigenvectors, containing the loadings of the original variables on the different PCs. $\mathbf{\Lambda}$ is a $(a \times a)$ diagonal matrix with the singular values $\lambda_j$ (for $j = 1, 2, \ldots, a$) as elements on the main diagonal. The singular values are the square roots of the eigenvalues. $\lambda_1$ is associated with the first principal component (PC1) and is related to the amount of variance explained by PC1. By definition $\lambda_1 \geq \lambda_2 \geq \cdots \geq \lambda_a$ so that the principal components can be said to describe decreasing amounts of variance (or information) in $\mathbf{X}$. A measure to indicate the percentage variance explained by each principal component is the contribution which is calculated as:

$$\text{Contrib}_{\text{PC}a} = \frac{\lambda_a^2}{\sum_{j=1}^{a} \lambda_j^2} \quad (3)$$

The first PCs will contain all the real information contained in the original data matrix $\mathbf{X}$, while the remaining PCs contain only noise (random variation). These first $r$ ($r < \min(m, p)$) PCs containing information are called significant or important PCs while the remaining $(a - r)$ PCs are called residual PCs (Eq. (4)).

$$\begin{aligned}\mathbf{X}_c(m \times p) &= \mathbf{T}(m \times r)\mathbf{V}^T(r \times p) \\ &\quad + \mathbf{T}(m(a-r))\mathbf{V}^T((a-r)p) \\ &= \mathbf{T}(m \times r)\mathbf{V}^T(r \times p) + \mathbf{E}(m \times p)\end{aligned} \quad (4)$$

where $\mathbf{E}$ is the matrix of the residuals.

Different methods such as the SCREE and LEV plot (Jackson, 1991), leave-one-out cross-validation (LOOCV) (Eastment and Krzanowski, 1982), Malinowski's IND (Malinowski, 1977, 1991) and REV functions (Malinowski, 1987; Faber and Kowalski, 1997) and the permutation test (Dijksterhuis and Heiser, 1995) are described in the literature to determine $r$. Different methods however often lead to different numbers of important PCs (Jackson, 1991), so that this determination is often uncertain.

### 2.3. Hotelling's $T^2$ test

Hotelling's $T^2$ test (Jackson, 1991; Tracy et al., 1992) is based on the use of the squared Mahalanobis distance (MD) which is computed as:

$$\text{MD}_i^2 = (\mathbf{x}_i - \bar{\mathbf{x}})\mathbf{C}_x^{-1}(\mathbf{x}_i - \bar{\mathbf{x}})^T \quad (5)$$

with $\mathbf{x}_i$ the vector corresponding with dissolution profile $i$, $\bar{\mathbf{x}}$ the vector of the means and $\mathbf{C}_x$ the variance–covariance matrix:

$$\mathbf{C}_x = \frac{1}{m-1}\mathbf{X}_c^T\mathbf{X}_c \quad (6)$$

with $\mathbf{X}_c$ the column centred matrix of $\mathbf{X}$, i.e. $(\mathbf{X}-\bar{\mathbf{X}})$.

The test can be used to detect outliers from the reference batch. Since the squared MD is always positive, usually only the upper confidence limit ($T^2_{UCL}$) is defined:

$$T^2_{UCL} \cong \frac{(m-1)^2}{m}\beta_{(\alpha;p/2,(m-p-1)/2)} \quad (7)$$

This limit is built using the β-distribution, which takes into account the fact that, if an outlier is present, the estimated mean $\bar{\mathbf{x}}$ and the variance–covariance matrix $\mathbf{C}_x$ for computing the MD, are already influenced by it. $T^2_{UCL}$ can also be computed using the $F$-distribution:

$$T^2_{UCL} = \frac{(m-1)^2}{m} \times \frac{(p/(m-p-1)F_{(\alpha;p,m-p-1)}}{1+(p/(m-p-1))F_{(\alpha;p,m-p-1)}} \quad (8)$$

with $F_{(\alpha;p,m-p-1)}$ the tabulated value of the $F$-distribution at significance level $\alpha$ and $p$ and $m-p-1$ degrees of freedom. The time point 0 may not be included in the computations since it contains no information (all percentages dissolved are equal to zero) while it anyway influences the number of degrees of freedom for building the limit.

Hotelling's $T^2$ test is also used to check whether the measurements of the test batch have a squared MD towards the central point of the reference set which is smaller than the limit defined as:

$$T^2_{UCL} = \frac{p(m-1)(m+1)}{m(m-p)}F_{(\alpha;p,m-p)} \quad (9)$$

For calculation of the MD of the test set measurements, $\bar{\mathbf{x}}$ and $\mathbf{C}_x$ of the reference set are used in Eq. (5).

It is also possible to use Hotelling's $T^2$ test following PCA. The aim of using the MD in the PC space is no longer to take into account the correlation between the variables (PCs are by definition orthogonal), but Hotelling's $T^2$ test has the property that each PC is weighted equally since the normalised scores are used:

$$T_i^2 = (m-1)\mathbf{u}_i(\mathbf{u}_i)^T = (m-1)\sum_{j=1}^{a}(\mathbf{u}_{ij})^2 \quad (10)$$

with $\mathbf{u}_i$ the normalised score vector of object $i$. $T_i^2$ can be calculated using all $a$ PCs, but mostly only the $r$ significant PCs are monitored (the total number of PCs $a$ in Eq. (10) is then replaced by $r$).

### 2.4. Area under the curve

The area under the curve (AUC) can be computed for each dissolution profile as the sum of the areas of the trapezia formed by the points $(t_{i-1}, 0)$, $(t_i, 0)$, $(t_{i-1}, y_{i-1})$ and $(t_i, y_i)$:

$$AUC = \sum_{i=1}^{p}\frac{(t_i - t_{i-1})(y_{i-1}+y_i)}{2} \quad (11)$$

with $t_i$ the dissolution time and $y_i$ the percentage of active dissolved at that dissolution time.

### 2.5. Resampling with replacement or bootstrapping

Starting from a matrix $\mathbf{X}$ $(m \times p)$, a new random matrix $\mathbf{X}_1$ $(m \times p)$ is generated by drawing with replacement $m$ rows from the original matrix $\mathbf{X}$ (Efron and Tibshirani, 1986; Shah et al., 1998). When this procedure is repeated $n$ times (e.g. 1000), it results in $n$ matrices ($\mathbf{X}_1$, $\mathbf{X}_2$, …, $\mathbf{X}_n$), all with size $(m \times p)$. After calculation of the vector of column means for each matrix, a $(n \times p)$ matrix is formed with these vectors.

### 2.6. Software

All programs used for the above-described methods were written in MATLAB (Version 4.0, the MathWorks, Natick, MA, USA).

## 3. Data

Data A were obtained from the industry and contain the dissolution profiles of four batches measured from tablets and capsules of a drug A. Each batch contains 12 dissolution profiles measured at 15, 30, 45 and 60 min with a USP apparatus II (rotating paddles) at 50 rpm in 900

ml of dissolution solution and using sinkers. Two batches contain the dissolution profiles from the original or reference tablets (Ar1 and Ar2) and the two other batches from the reformulated or test capsules (At1 and At2), all tested under the same conditions. The dissolution profiles of the reference set Ar1, together with the mean profiles for Ar1 and At1 are shown in Fig. 1.

Data B were published earlier by Tsong and Hammerstrom (1994). Twelve units of both a reference (Br1) and a test batch (Bt1) were measured at seven different times (1, 2, 3, 4, 6, 8 and 10 h). Fig. 2 shows the dissolution profiles of Br1 together with the mean profiles of Br1 and Bt1.

## 4. Results and discussion

### 4.1. The similarity factor

First the dissolution profiles of the reference tablets Ar1 and the reformulation capsules At1 are compared. For the similarity factor $f_2$ the advice not to include points with a dissolution higher than 85% (Shah et al., 1998), is not followed since at most time points the dissolution profiles reach a higher dissolution (see Fig. 1) and there still is a relatively high variation between the dissolution profiles. To compare the reformulated batch with the reference batch, $f_2$ is computed using their mean dissolution profiles. The $f_2$ computed in this way has a value of 83, which is clearly higher than the critical limit of 50 so that the two batches can be considered not to be pharmaceutically different. Also, when each of the dissolution profiles of the reformulated capsules is compared separately with the mean dissolution profile of the reference batch, all profiles pass the requirement ($f_2 > 50$).

Compared with data A, data B (Br1 and Bt1) are measured at seven instead of four time points and, for the reference batch, only at the last time point the mean percentage dissolved is higher than 85%. The $f_2$ calculated using the mean disso-

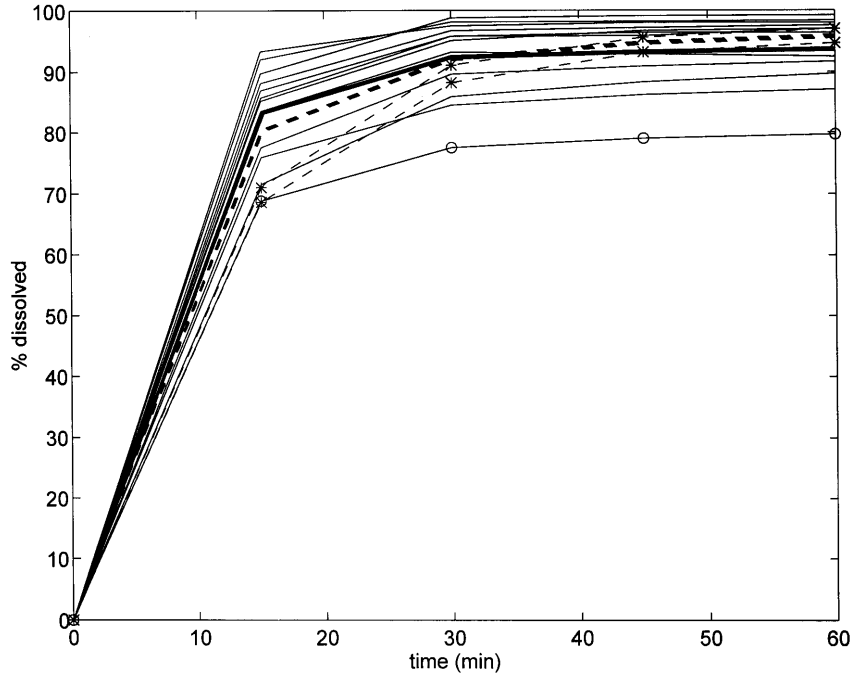


Fig. 1. The 12 dissolution profiles of the tablets of the reference set (Ar1) with dissolution profile 8 indicated with the (—○—) symbol and two dissolution profiles (2 and 7) of the capsules of the reformulated batch (At1) indicated with the (- -*- -) symbol. The solid bold line represents the mean reference profile and the dashed bold line the mean test profile.

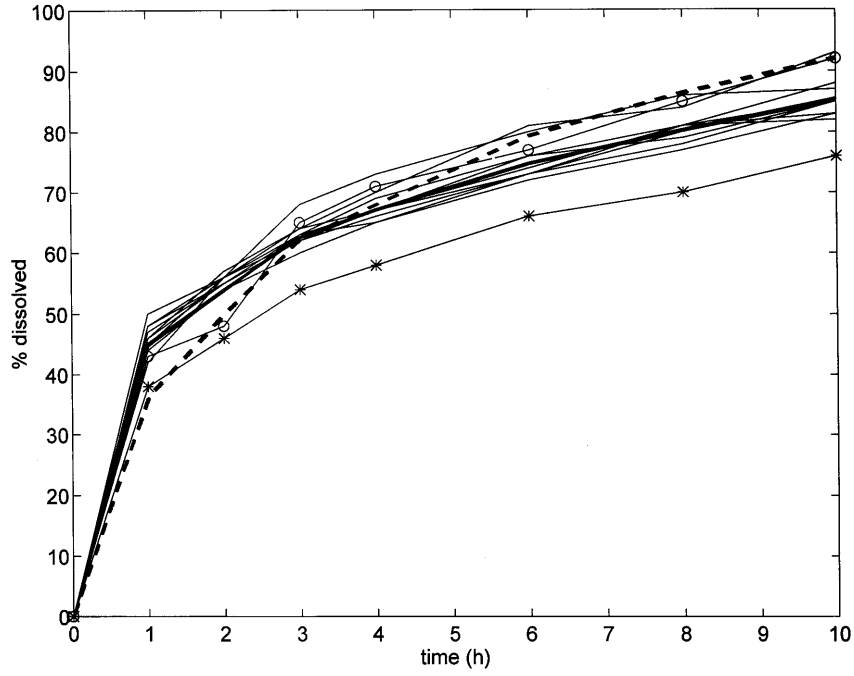


Fig. 2. The dissolution profiles of the reference batch Br1. Dissolution profile 2 is indicated with (—○—) and profile 9 with (- -*- -). The solid bold line represents the mean reference profile and the dashed bold line the mean test profile.

lution profiles has a value of 64. Since this value is higher than the limit of 50, the two batches can be considered similar. When each dissolution profile of the test batch was compared with the mean of the reference batch, all $f_2$ values were higher than 50.

To achieve some insight into the within-batch variability it is useful to check whether there are profiles in the reference batch, which are different from the rest. Using the leave-one-out (LOO) principle, the first dissolution profile of the reference batch is tested against the mean of the remaining dissolution profiles of the reference batch. This is repeated for each profile in the reference batch. Computed in this way only profile 8 of Ar1 has a $f_2$ value lower than 50, namely 40. It can be seen in Fig. 1 that the eighth dissolution profile of the reference batch, indicated by the (○) symbol, is parallel with the other profiles of the reference batch, but that its percentage dissolved is systematically lower. The outlier can indicate a lack of robustness of the dissolution method or the manufacturing method of the dosage forms. When object 8 is removed and the LOO procedure is repeated, the mean of the reference batch is changed but all dissolution profiles of the reformulation batch still have $f_2$ values higher than 50.

All $f_2$ values, calculated by the LOO principle, for the different dissolution profiles of Br1 were larger than 50. Profile 9 has the lowest value: 51. It can be seen in Fig. 2 that for the ninth dissolution profile, indicated by the (*) symbol, the percentage dissolved is systematically lower than for the other profiles.

### 4.2. Hotelling's $T^2$ test to detect outliers

Hotelling's $T^2$ test using β-limits (Tracy et al., 1992) was also used to detect outliers from the reference batch. As shown in Fig. 3, no outliers are detected in the training set Ar1 ($\alpha = 0.01$). Objects 3 and 5 were found to be the worst correlated with the other curves of the reference set. Further analysis of these two profiles revealed that this is only due to some small anomalies in

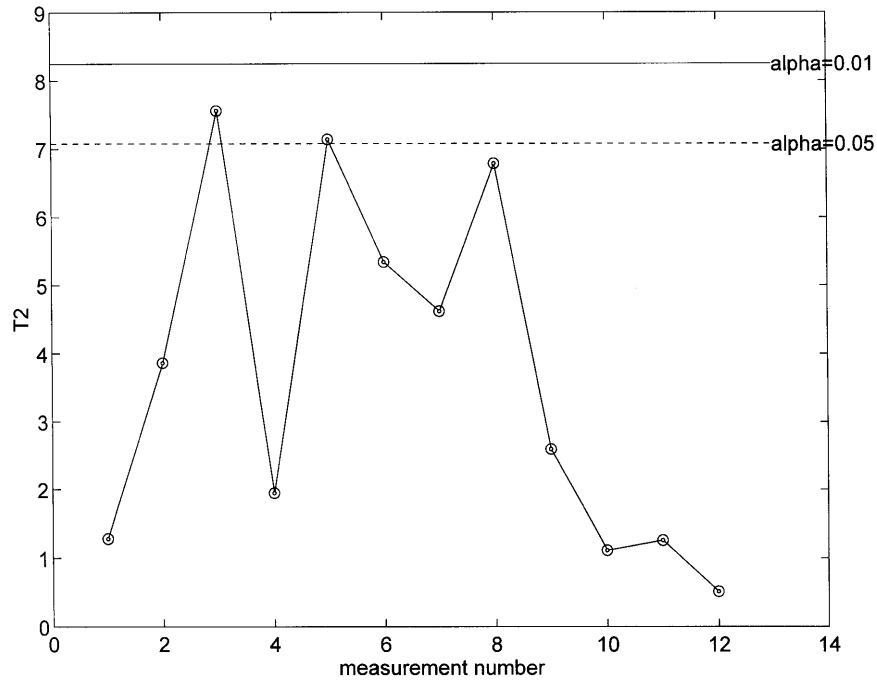


Fig. 3. Hotelling's $T^2$ test using the original variables for the dissolution profiles of the reference batch (Ar1).

the horizontal part of the curves (last two time points). On the other hand, object 8 which has a lower, but parallel profile compared with the other ones, is not detected as an outlier. In reference set Br1 too, no object is detected as an outlier ($\alpha = 0.05$) although object 9, indicated by the (*) symbol in Fig. 2, has a systematically lower profile. Dissolution curve 2, indicated by the (○) symbol in Fig. 2, is found to be the worst correlated. It can be concluded that Hotelling's $T^2$ test is not practically useful for the detection of outlying dissolution profiles because it is not sensitive enough to differences in the level of the curves and too sensitive to small deviations of the correlation.

### 4.3. Principal component analysis

The reference and test batches were compared with each other using PCA after column centring. The PC space was constructed using the reference batch and the test batch was projected in that space. Fig. 4 shows the PC1/PC2 scores plot of the dissolution curves of Ar1 and At1. This figure can be interpreted as follows: from the left to the right (along PC1) the level of the dissolution profiles increases. This is also reflected in the AUCs reported in Table 1. Fig. 4 shows that

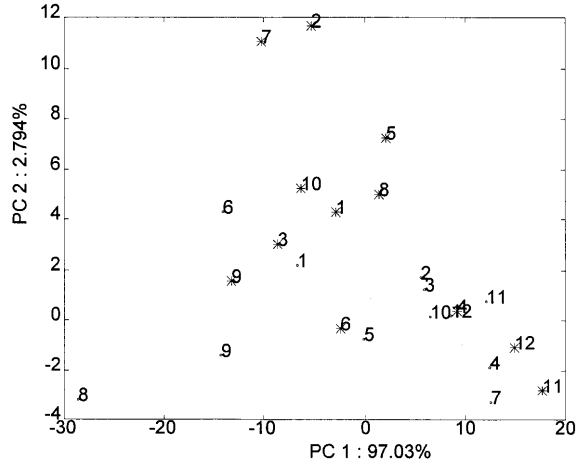


Fig. 4. The PCA scores plots of the dissolution profiles of the reference batch Ar1 (.) together with the projections of the dissolution profiles of the reformulation batch At1 (*). The contribution (%) of each PC is also indicated.

Table 1
Areas under the curve (AUC, % min) for batches Ar1, At1, Br1, Bt1

| Profile | Ar1 | At1 | Br1 | Bt1 |
|---|---|---|---|---|
| 1 | 4558 | 4658 | 42 150 | 39 000 |
| 2 | 4883 | 4593 | 40 710 | 40 710 |
| 3 | 4889 | 4499 | 39 210 | 39 570 |
| 4 | 5063 | 4978 | 41 760 | 39 030 |
| 5 | 4738 | 4785 | 39 870 | 39 480 |
| 6 | 4358 | 4667 | 39 750 | 42 510 |
| 7 | 5067 | 4460 | 39 390 | 40 290 |
| 8 | 3977 | 4772 | 38 190 | 39 900 |
| 9 | 4352 | 4382 | 34 380 | 40 770 |
| 10 | 4910 | 4567 | 39 150 | 40 800 |
| 11 | 5058 | 5198 | 39 810 | 41 730 |
| 12 | 4962 | 5124 | 39 060 | 41 580 |

along PC1 object 8 of the reference batch is located far away from the other objects of that batch. As already described, the eighth dissolution profile of reference batch Ar1 is parallel with the other objects of the set, but at each time point, the percentage dissolution is systematically lower. Along PC2, differences in the shape of the dissolution curves can be detected. Objects 2 and 7 of the reformulation batch At1 have much higher scores than the objects of the reference batch. In Fig. 1 the dissolution profiles of the second and seventh reformulated capsules (At1) were plotted together with the dissolution profiles of the reference batch (Ar1). It can be seen that, compared with the dissolution profiles of the reference batch, at 10 min these profiles have a relatively low dissolution, while at 60 min their dissolution is relatively high. To investigate whether the observed differences between the reference and reformulated batches are not just due to the batch-to-batch variation, the dissolution profiles of the two reference batches (Ar1 and Ar2) were analysed together. The two reference batches overlap well on the different PCs, indicating that the between-batch variation is small. The two reformulated batches (At1 and At2) were projected in that PC space as shown in Fig. 5.

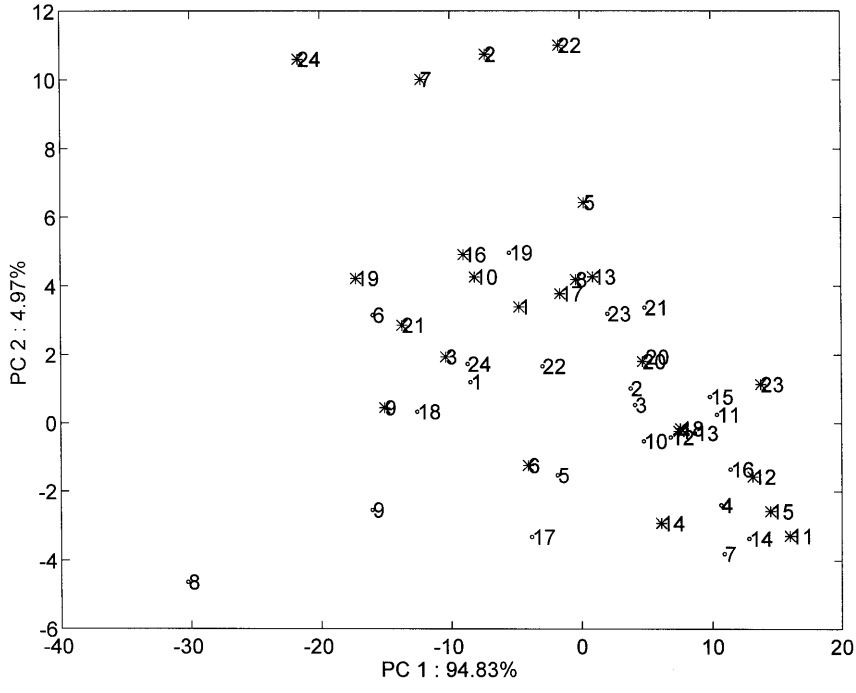


Fig. 5. The scores plots after PCA of the dissolution profiles of the two reference batches (.1–12 (Ar1) and .13–24 (Ar2)) together with the projections of the dissolution profiles of the two reformulation batches (*1–12 (At1) and *13–24 (At2)). The contribution (%) of each PC is also indicated.

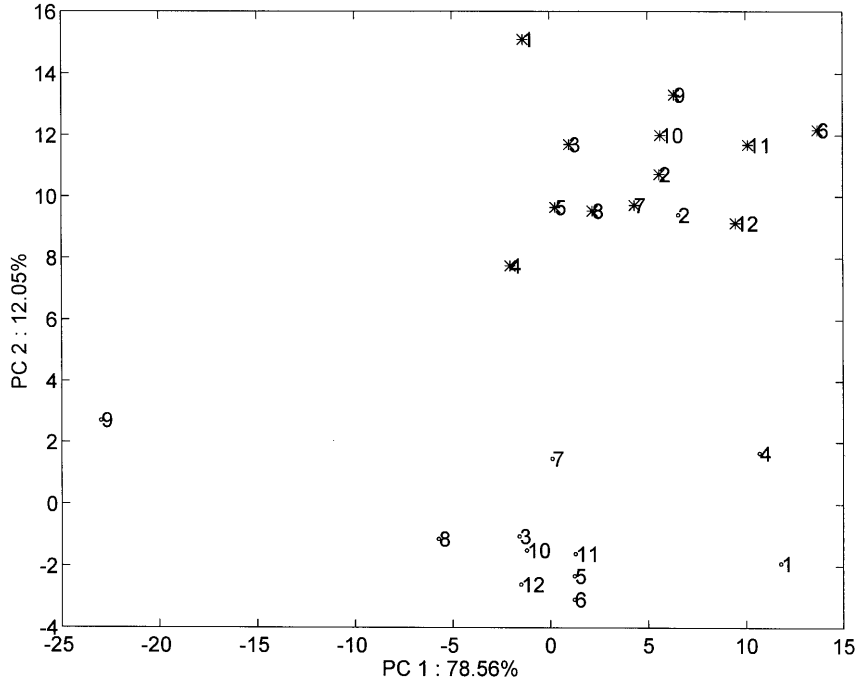


Fig. 6. The PCA scores plots of the dissolution profiles of the reference batch Br1 (.) together with the projections of the dissolution profiles of the test batch Bt1 (*). The symbol (%) expresses the contribution of each PC.

Analysis of the batches Br1 and Bt1 by PCA, showed that the level of the ninth dissolution profile of the reference batch Br1 differs from the other along PC1 (Fig. 6). The scores along PC1 correspond to the AUCs given in Table 1. Along PC2 object 2 of Br1 has much higher scores than the other objects of that batch. In Fig. 2, it can be seen that the second dissolution profile has a different shape compared with others.

Fig. 6 shows that the general shape of the dissolution profiles of batch Bt1 is clearly different from that of batch Br1.

### 4.4. Construction of the confidence limits using bootstrapping

To be able to reach a statistically based conclusion, the distribution of the $f_2$ factor is simulated using the resampling with replacement or bootstrap method as described in Section 2.5. The resampling with replacement technique was applied to both the reference and the test batch. Using the two $(n \times p)$ matrices of the column means vectors, $n$ $f_2$ factors are calculated by comparing the corresponding rows. A 95% lower confidence limit (LCL) is constructed by sorting the $n$ $f_2$ values and omitting the lower 5% (i.e. 50 values). A robust distribution is obtained for $n = 1000$. For batches Ar1 and At1, the 95% LCL amounts to 64.5 and for batches Br1 and Bt1 to 59.8. For both data A and B, the 95% LCL is higher than the similarity criterion of 50 so that the batches Ar1–At1 and Br1–Bt1 can be accepted as similar.

The resampling with replacement technique followed by PCA on the $(n \times p)$ matrix of the column means vectors can be used to simulate the distribution of the scores in the PC space. For $n = 1000$, this yields a normalised scores plot for the reference batch (Ar1) together with the projections of the dissolution profiles of the reformulated batch (At1) as shown in Fig. 7. A 95% confidence limit (CL) for the reference batch can be calculated using Hotelling's $T^2$ test for two PCs. For each of the 1000 column mean vectors obtained, the $T^2$ value was computed. After sort-

ing these values, the upper 50 (5%) were omitted. This is also shown in Fig. 7 where the 95% CL is indicated by the circle. As can be seen, there is only little overlap between the two batches. Since there are nearly no differences along PC1, the level of the batches can be considered to be equal, but along PC2 it can be seen that a difference in shape is noticed. Although the latter is somewhat exaggerated, the assessments obtained with the PCA/bootstrap technique conform to what is shown in Fig. 1.

The same was done for the reference (Br1) and the reformulated batch (Bt1) as shown in Fig. 8. As can be seen, there is no overlap between the two batches. The slight difference along PC1 indicates that the level of the two batches is nearly equal. However, along PC2 a considerable difference can be observed which means that the shape of the profiles of the two batches is different. Here too the difference in shape is probably somewhat overinterpreted, but in general the conclusions agree with the mean profiles shown in Fig. 2 and with the results of Fig. 6.

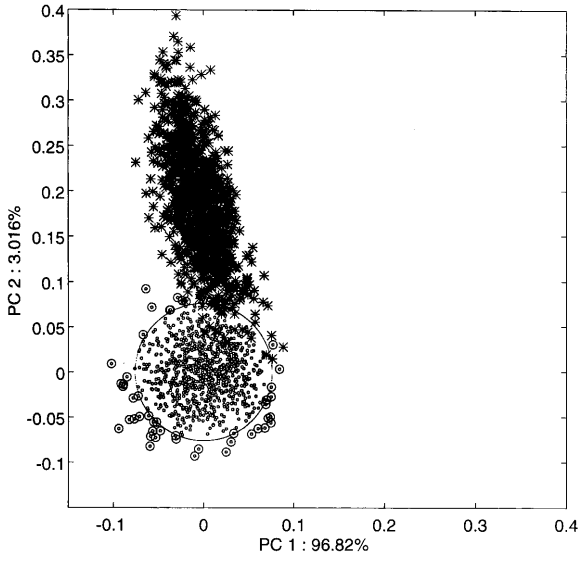


Fig. 7. The PCA normalised scores plots after resampling with replacement ($n = 1000$) for the reference batch Ar1 (.) together with the projections of the dissolution profiles of the reformulation batch At1 (*). The 95% confidence limit for the reference batch is indicated by the circle and the 5% omitted objects are indicated by ( ⊙ ). The contribution (%) of each PC is also indicated.

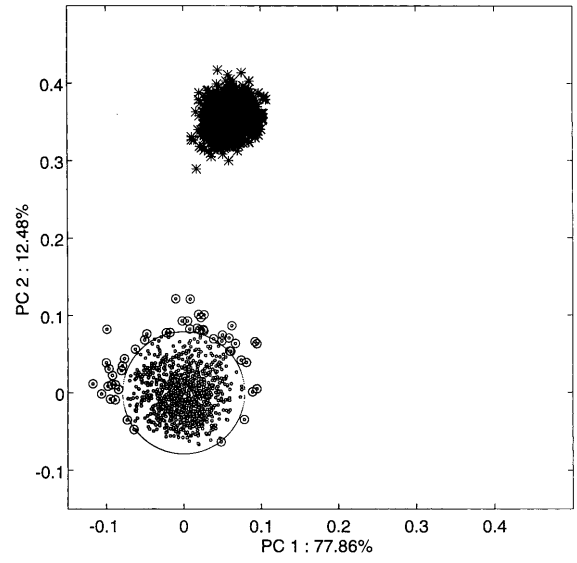


Fig. 8. The PCA normalised scores plots after resampling with replacement ($n = 1000$) for the reference batch Br1 (.) together with the projections of the dissolution profiles of the reformulation batch Bt1 (*). The 95% confidence limit for the reference batch is indicated by the circle and the 5% omitted objects are indicated by ( ⊙ ). The contribution (%) of each PC is also indicated

### 4.5. Study of the limit of the similarity factor ($f_2 = 50$) by PCA

As mentioned in Section 2.1, the $f_2$ limit value of 50 was obtained by assuming a 10% average difference at any measurement time point. For four time points (as for batch Ar1), this means that the sum of the squared differences in Eq. (1) is $10^2 + 10^2 + 10^2 + 10^2 = 400$. First, all 16 possible combinations with a + or − 10% difference in each of the four time points compared with the mean of the reference batch (Ar1) were generated, followed by the eight possibilities with a + or − 20% difference in one of the four time points. After column centring, these 24 simulated curves were projected in the PC space defined by the reference set. Six of the 24 curves, corresponding to profiles 1–6 in Table 2 and points 1–6 in Fig. 9, form the borderline. To examine the shape (circle, hexagon, …) of this borderline, about 200 profiles (in the neighbourhood of and between the above-mentioned six border points) were gener-

Table 2
Percentage difference (%) of eight dissolution profiles (*1–8 in Fig. 9) at four time points, resulting in a $f_2 = 50$ compared with the mean of the reference batch (Ar1)[a]

| Profile | % at 15 min | % at 30 min | % at 45 min | % at 60 min | AUC |
|---|---|---|---|---|---|
| 1 | +10 | +10 | +10 | +10 | 5260 |
| 2 | −10 | +10 | +10 | +10 | 4960 |
| 3 | −20 | 0 | 0 | 0 | 4435 |
| 4 | −10 | −10 | −10 | −10 | 4210 |
| 5 | +10 | −10 | −10 | −10 | 4510 |
| 6 | +20 | 0 | 0 | 0 | 5035 |
| 7 | +10 | −10 | −10 | +10 | 4660 |
| 8 | 0 | 0 | +20 | 0 | 5035 |

[a] The last column contains the areas under the curve (AUC, % min).

ated, all with a sum of squared differences equal to 400 towards the mean of the reference batch (Ar1). When those curves were projected in the PC space built by the reference set, they were all located in an area limited by a circle. Fig. 9 gives an overview, showing the PC1/PC2 scores plot of the 12 dissolution profiles of the reference batch together with the limiting circle for dissolution profiles with a $f_2 = 50$. As can be seen, object 8 of the reference batch Ar1 (.8) with a $f_2$ value of 40, calculated by LOO, is outside the circle. The six points of the circle (*1–6) as well as *7 and *8 will be discussed more in detail. The percentage differences for dissolution profiles *7 and *8 compared with the mean of the reference batch are also given in Table 2. Fig. 9 can be interpreted as Figs. 6 and 8: PC1 indicates the level of the dissolution profiles, which is also reflected in the AUCs (Table 2) and along PC2 differences in the shape of the dissolution curves can be detected. Points *5 and *6 represent dissolution profiles that start higher and end equal (*6) or lower (*5) than the reference one. Points *1 and *4 have low scores on PC2 since they correspond to curves that are about parallel with the reference (10% higher (*1) and 10% lower (*4)). Points *2 and *3 represent profiles that start lower and end higher (*2) or equal (*3) than the reference curve. Points *7 and *8 are examples of profiles with a $f_2$ value of 50 versus the reference set which do not lie on, but inside the circle, which means that the difference in dissolution found in the $f_2$ factor is not fully reflected in the PC1/PC2 scores plot. The dissolution curves corresponding to these two points (see also Table 2) show irregularities like going up, down and up again (*7) or a strongly deviant percentage at one time point in the middle (*8). Therefore, although these irregularities have a strong influence on the $f_2$ factor, they are filtered out in the PC1/PC2 scores plot. They can, if one wishes to, be detected by their high residual from the PC1/PC2 model using methods such as SIMCA (Wold and Sjöström, 1977).

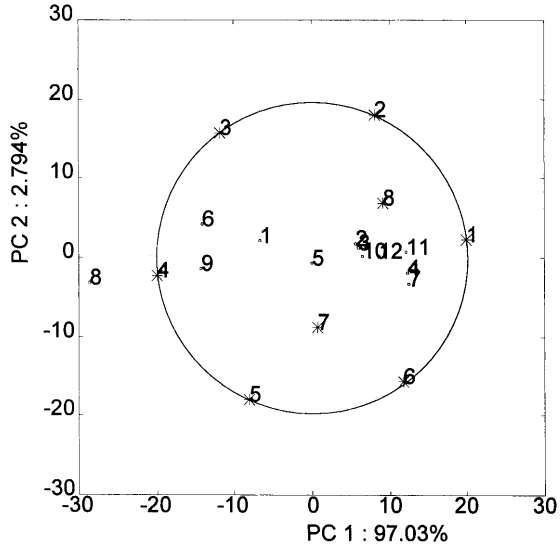


Fig. 9. The PCA scores plots of the dissolution profiles of the reference set Ar1 (.) together with the projections of some simulated dissolution profiles with a $f_2$ value of 50 (*), limited by a circle. The contribution (%) of each PC is also indicated.

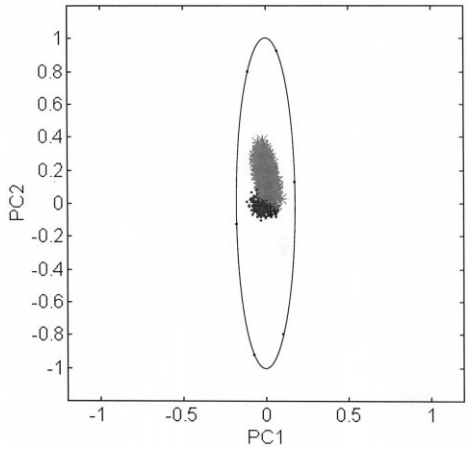


Fig. 10. The PCA normalised scores plots after resampling with replacement ($n = 1000$) for the reference batch Ar1 (.) together with the projections of the dissolution profiles of the reformulation batch At1 (*) and the limiting ellipse for profiles with a $f_2$ value of 50.

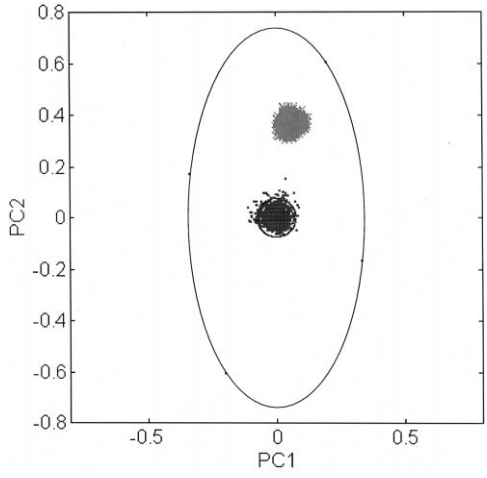


Fig. 11. The PCA normalised scores plots after resampling with replacement ($n = 1000$) for the reference batch Br1 (.) together with the projections of the dissolution profiles of the reformulation batch Bt1 (*) and the limiting ellipse for profiles with a $f_2$ value of 50.

The limiting values for $f_2 = 50$ are also plotted on the PC1/PC2 normalised scores plot of Fig. 7, as shown in Fig. 10. Since normalised scores are used here, the limiting circle of Fig. 9 is now an ellipse. As can be seen, the bootstrapped test batch (At1) falls completely inside the ellipse so that both batches can be considered similar from a pharmaceutical point of view. An analogous result was obtained for data B (Fig. 11).

## 5. Conclusion

The dissolution profiles from a batch of reformulated capsules were compared with those of a batch of reference tablets using the $f_2$ factor and PCA. Using the similarity factor $f_2$, recommended by the FDA, the reformulated dissolution profiles are considered to be equal to the reference set.

Using PCA, the dissolution profiles with a systematically higher or lower percentage dissolution at each time point can be recognised along PC1 in the scores plot. Along PC2 the dissolution profiles with a different shape can be seen. Although PCA is a powerful tool to visually explore the dissolution data, it contains no decision criteria. This can be achieved by combining PCA with the resampling with replacement or bootstrap technique.

The study of dissolution curves with a $f_2$ value of 50 by PCA revealed that the similarity factor is sensitive to irrelevant deviations, but that these irregularities are filtered out in the PC1/PC2 scores plot. One can criticise the choice of the 10% average difference allowed between two batches because this value is arbitrarily chosen and should be useful for all types of tablets and drugs. It might be preferable to set separate limits for the level and the shape of the dissolution curves. The separation between level and shape can be performed using PCA.

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