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Use of control sample for estimation of prediction error in multivariate determination of lidocaine solutions with non-column chromatographic diode array UV spectroscopy

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Abstract

The aim of this study was to investigate the ability of a control sample, of known content and identity, to diagnose and correct errors in the predictions when the same multivariate calibration model was used for analysis of new samples over time. A calibration set consisting of 16 samples with a known content of lidocaine was analysed and two external test sets, A and B, were used for the validation. Test set A contained 15 samples with different concentrations of lidocaine and test set B contained three samples with different lidocaine content, which were analysed six times in order to obtain a measure of repeatability. The multivariate calibration was done with PLS regression on UV spectra collected between 245 and 290 nm. A representative UV spectrum was exported from the collected DAD files by two methods, average spectrum over the whole file and average spectrum over the sample plug. Test set A was analysed further on another three occasions together with a control sample. The results showed that the control sample could be used to give a diagnosis and estimate of the prediction error. Moreover, the measured prediction error of the control sample could also be used to correct the predictions, thereby reducing the prediction error. Finally, some practical considerations regarding use of the proposed DAD method with a control sample are presented. The procedure suggested could lead to an efficient analytical approach where the same calibration model could be used over time without recalibration, which may be attractive in industrial quality control or screening analysis in pharmaceutical research.

Keywords: Control sample; Non-column; Diode array UV spectroscopy; Multivariate calibration; Lidocaine

1. Introduction

The determination of pharmaceutical substances in solution can be done with various analytical methods. In the pharmaceutical industry high-

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performance liquid chromatography (HPLC) with external standards is often employed for this analysis. In fact, even though HPLC is a separation technique, it is often used for the analysis of samples that do not need any separation, i.e. solutions containing only one dissolved substance. For pharmaceutical solutions of this type, spectrometric analysis with multivariate calibration is an alternative to HPLC.

When a multivariate calibration model is constructed on one occasion and used for the prediction of new samples on later occasions, there is always some influence from small variations in the instrumental parameters, which can lead to errors in the predictions obtained. If samples are measured on a different instrument or under different conditions than the calibration samples, this also affects the reliability of the predictions. For the latter problem, various chemometric methods for calibration transfer between instruments have been presented [1]. These methods include procedures to be used before the calibration model is implemented such as instrument matching [2], global models including all expected sources of variance, model-updating techniques by adding new samples and sensor selection using variables less sensitive to variations in the experimental conditions [3]. When a calibration model is in use, different methods to compensate for non-calibrated variations have also been described. Here instrument standardisation is common where a new set of samples is analysed on the different instruments and the results obtained are used to standardise the predicted values [4], the regression coefficients or the spectral responses [5].

A possible way to obtain diagnostic information about the reliability of the predictions is to use a sample of known content and identity, a control sample, and to analyse it together with the other samples. By comparing the accepted reference value of the control sample with the predicted value it should be possible to obtain diagnostic information about how reliable the predictions are. This analytical procedure could be a simple and straightforward approach, although the use of control samples together with multivariate calibration is not common in the literature. Another way to detect poor predictions and outliers in multivariate calibration is to analyse how well the new samples fit into the calibration model, i.e. to use the residuals. Using multivariate residuals as well as a control sample could be a way of implementing multivariate spectrometric determinations of pharmaceutical solutions with the same calibration model over time. The use of residuals was discussed in a previous paper, in which the idea of control samples was also briefly introduced [6].

Another approach to the problem of calibration transfer is to try to minimise it by simplifying the analytical process as much as possible. With the aid of automation, the spectrometric analysis of pharmaceutical solutions containing only a few ingredients can be simplified. Previously, a method for the determination of lidocaine with scanning UV–Vis spectroscopy and multivariate calibration was presented [6]. This method was further developed with non-column chromatographic diode array UV spectroscopy using a conventional HPLC–DAD system without separation, giving a fast analytical method with a high degree of automation [7]. In the following text the non-column diode array UV spectroscopy is referred to as the DAD method.

The aims of the following study were to investigate the ability of a control sample to diagnose errors in the predictions when a calibration model is used over time and to investigate whether the predictions of the samples can be corrected with the help of the known prediction error of a control sample. A further aim was to outline the practical procedure for the use of control samples together with the DAD method.

In this study plain lidocaine solutions were used as a simple and well-known [6,7] model solution on which to test the idea of control samples.

2. Experimental

2.1. Instrumentation

The HPLC was a Dionex Summit with the chromatographic data system Chromeleon version 6.11. A Dionex PDA 100 Diode Array Detector with a wavelength range of 190–800 nm was used with the bandwidth 1 nm. The autosampler in the

system was a Dionex ASI 100T and the pump a binary high-pressure gradient pump, Dionex P580HPG.

When non-column chromatographic diode array detection was used, a back-pressure tube (PEEK, id 0.1 mm, length 6 m) was connected between the autosampler and the detector to obtain a pressure for the pump to work against and purified water (Waters Milli-Q) was used as eluent.

The UV spectra were collected in the same wavelength interval as in previous investigations, 245–290 nm [6,7]. The structure and UV spectrum of lidocaine are described in Fig. 1. The multivariate calibration with partial least squares regression (PLS) [8,9] was done using the software Simca-P 8.1 (Umetrics).

The instrumental setting was taken from an experimental design study carried out in a previous investigation, with flow 1.5 ml min^{-1}, data-collection rate 10 Hz, rise time 1 s, data-sampling time 0.5 min and spectral resolution 1 nm [7]. The rise time is defined in Chromeleon as the time taken for the output signal to rise from 10 to 90% of its final value [10].

The preparation of the calibration and test set samples was done by weighing lidocaine into stock solutions with a calibrated balance, Sartorius MC5, and then further diluting these solutions with an automatic diluter, Hamilton Microlab 1000, to the desired concentrations.

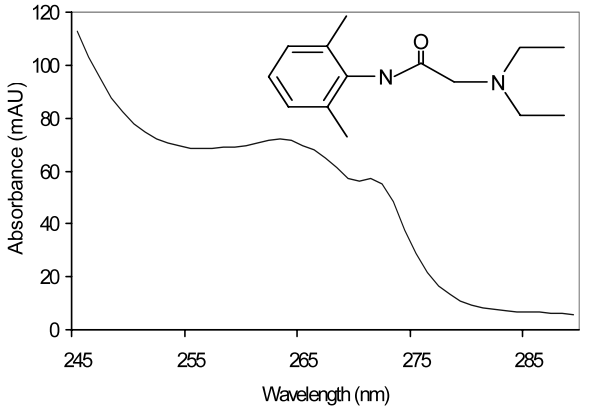

Fig. 1. UV spectra (245–290 nm) and structural formula of lidocaine (0.15 mg ml^{-1}) in Milli-Q water.

2.2. Reagents

Analytical grade chemicals were used throughout the study. The water used was HPLC grade water provided by a Millipore Milli-Q filtration/purification system.

AstraZeneca Bulk Production Södertälje supplied lidocaine hydrochloride. The lidocaine solutions used in the study were made by weighing and dissolving the substance in Milli-Q water and further dilution to the concentration range 0.15–0.3 mg ml^{-1}.

2.3. Data sampling

The shape of the data sampled with a DAD has one main difference compared to scanning UV–Vis spectroscopy. While the scanning spectrophotometer measures the absorbance as a function of wavelength, the DAD has one further dimension, time. Hence the data resulting from a DAD analysis can be viewed as a number of UV–Vis spectra collected over a time interval, the sampling time. The rate at which spectra are collected is controlled by the data-collection rate. In this study a data-collection rate of 10 Hz and a sampling time of 30 s gave about 300 spectra in each collected DAD file. The wavelength region chosen, 245–290 nm, gave, with a resolution of 1 nm, 46 variables. If multivariate calibration with ordinary PLS is to take place on DAD data from a number of samples, it is essential to transform the data of each sample into a two-dimensional matrix. This can be done by unfolding, where an $A \times B \times C$ array is unfolded, for instance, to an $A \times BC$ matrix [11]. Another approach is to reduce the data to a two-dimensional matrix. This means finding a way to export a representative UV–Vis spectrum from the collected DAD file (Fig. 2). One way of doing this is to export the spectrum at the maximum intensity time (SMIT) (Fig. 2a), while another is to calculate an average spectrum. By calculating the average of all the spectra collected, an average spectrum for the whole DAD file can be obtained (Fig. 2c). Exporting the spectrum at SMIT and calculating an average spectrum of the whole DAD file was investigated in a previous study, which gave roughly equal prediction results

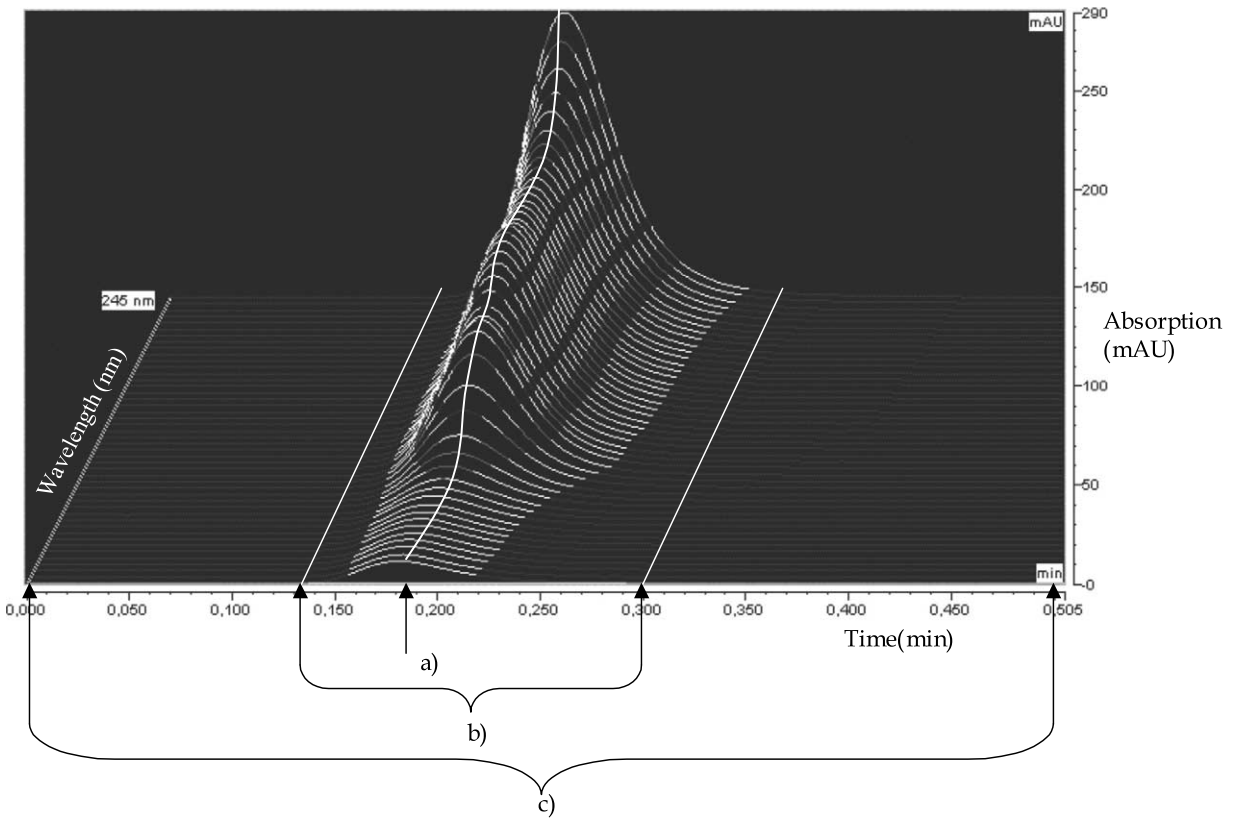

Fig. 2. Schematic image of the three approaches to export a representative UV spectrum from a collected DAD file. The 3D image is taken from Chromeleon version 6.11. (a) UV spectrum at spectrum maximum intensity time (SMIT), (b) average UV spectrum over sample peak, (c) average UV spectum over whole DAD file.

[7]. A third approach is to calculate the average spectrum for the part of the DAD file that contains the spectra of the sample of interest, i.e. in a solution containing only one substance the average spectrum over the sample plug (Fig. 2b). Calculating the average spectrum only over the sample plug, when the sample is actually in the sample cell, could be one way of reducing the influence of noise coming from parts of the DAD file that do not contain spectra of the sample of interest. In this study, the average spectrum for the whole collected DAD file as well as for the sample plug was used.

With a flow rate of 1.5 ml min^{-1}, the lidocaine sample plug was about 0.15 min wide and the time interval for the calculation of the average over the sample plug chosen was 0.13–0.3 min (Fig. 2). This interval was chosen since some minor variation of the SMIT was observed ($\pm$1 s). Hence a somewhat too wide time interval was applied to take account of this small variation. With the data-collection rate used, this gives about 100 spectra in this time interval.

A representative UV spectrum of each collected DAD file was exported with the two different file-export methods with the help of macros written in MS Excel.

After the analysis of the samples with the different methods, the spectra were exported to the software Simca-P 8.1, in which PLS calibration models and predictions were made. All the data were mean-centred before modelling and all the

PLS models used in the study contained one PLS component that explained >99% of the variation in the data.

2.4. Calibration set and control sample

A calibration set of 16 samples was constructed containing 0.15–0.3 mg ml^{-1} lidocaine. The lidocaine concentration of these samples varied by a fixed step (i.e. 0.150, 0.160, 0.170 mg ml^{-1} etc). This concentration range was chosen since it had been used in a previous study [7]. The calibration set was used for construction of the calibration model used in the study. Control samples containing 0.22 mg ml^{-1} lidocaine were also prepared in conjunction with the calibration samples.

2.5. Validation

The calibration models were validated with two external test sets (A and B). Test set A contained 15 samples with different amounts of lidocaine in the range 0.15–0.3 mg ml^{-1}. Test set B contained three samples with different amounts of lidocaine—0.166, 0.227 and 0.296 mg ml^{-1}—that were analysed six times to obtain a measure of repeatability. The calibration set and the samples in test set A and B were analysed on the same occasion. Six repeated analyses of a control sample were also made on this occasion.

Test set A was analysed further on another three occasions to investigate whether the use of a control sample could estimate and correct for the prediction error when the same calibration model was used over time. These analyses were performed 1–3 weeks after the calibration model had been made. In this part of the study the average spectrum over the whole DAD file was exported and used. The same samples were analysed on these three occasions and in between the analyses they were stored in a refrigerator.

For the evaluation of the predictive ability of the samples in test set A, the root mean square error of prediction (RMSEP) [12] and relative standard error of prediction (RSEP) [13] were calculated.

$$\mathrm{RMSEP} = \sqrt{\frac{\sum_{i=1}^{n} (y_{\mathrm{pred}} - y_{\mathrm{obs}})^2}{n}}, \quad (1)$$

$$\mathrm{RSEP}(\%) = 100 \times \sqrt{\frac{\sum_{i=1}^{n} (y_{\mathrm{pred}} - y_{\mathrm{obs}})^2}{\sum_{i=1}^{n} (y_{\mathrm{obs}})^2}}, \quad (2)$$

where y_{pred} is the predicted concentration in the sample, y_{obs} is the observed or reference value of the concentration in the sample and n is the number of samples in the test set.

3. Result and discussion

In Table 1 the predictions of the samples in external test set A are shown. These results come from analysis where the calibration set and the test sets were analysed on the same occasion and the predictions for the two ways of exporting a representative UV spectrum from the DAD file are presented. The RMSEP and RSEP are presented for each set of predictions of the samples in test set A.

From the results in Table 1 it can be seen that the average spectrum over the sample plug gave slightly better results than the average spectrum over the whole DAD file. One possible explanation for this is the following. The average UV spectrum calculated over the whole collected DAD file is an average spectrum calculated from about 300 spectra. Of these 300 spectra, less than 100 contain a UV spectrum of lidocaine since the sample plug with this instrumental setting is about 0.15 min wide (Fig. 2). Hence more than 200 of the spectra in the DAD file contain noise since no lidocaine is analysed. At the beginning of the DAD file there is also a small injection disturbance caused by the injection of the sample with the autoinjector. If an average spectrum of the whole DAD file is calculated, this means that this noise is added to the average UV spectrum calculated. An average spectrum only over the sample peak probably reduces the influence of this noise.

Table 1
Prediction results of the samples in external test set A

Sample number	Accepted reference value	Predicted concentration (mg ml^{-1})	
		DAD method (average spectrum)	DAD method (average spectrum sample plug)
1	0.153	0.151	0.153
2	0.166	0.162	0.164
3	0.175	0.173	0.175
4	0.186	0.185	0.186
5	0.198	0.197	0.198
6	0.205	0.205	0.206
7	0.216	0.215	0.217
8	0.227	0.228	0.228
9	0.238	0.238	0.238
10	0.246	0.244	0.246
11	0.256	0.254	0.256
12	0.269	0.270	0.271
13	0.276	0.275	0.276
14	0.286	0.284	0.287
15	0.296	0.299	0.298
RMSEP		0.0018	0.0011
RSEP (%)		0.83	0.46

In Table 2 the results of the repeatability study are shown. Three samples with different concentrations of lidocaine were each analysed six times. The relative standard deviation (RSD) is presented. As can be seen in Table 2, the two file export methods gave similar results, with a RSD of $< 0.8\%$ at the lowest concentration. This precision is somewhat worse compared to a previous study where a scanning spectrophotometer was used [6]. In this study six repeated analyses of a solution containing 0.18 mg ml^{-1} lidocaine gave an RSD of about 0.05%. One possible explanation for this might be the dynamic sample compartment in the DAD, where liquid is constantly flowing through the detector cell. In this study this analysis was done using six injections with the autosampler, which probably induces some instrumental variation in the analysis.

Table 2
Repeatability of prediction results of the samples in external test set B

Instrument	Accepted reference value	RSD of six replicates (%)
DAD method (average spectrum)	0.166	0.78
	0.227	0.50
	0.296	0.26
DAD method (average spectrum sample plug)	0.166	0.71
	0.227	0.20
	0.296	0.31

RSD, Relative standard deviation.

Table 3 shows the predictions of the samples in test set A as well as the control sample on three different occasions analysed with the DAD method using the average spectrum for the whole DAD files. These analyses were done 1–3 weeks after the calibration set in order to test the ability of a single control sample to diagnose the reliability of the predictions over time. The result shows that predictions could be made over time with a reasonably low prediction error (RMSEP < 0.006 and RSEP $< 2.3\%$). These results can be compared with the results obtained for the average spectrum of the whole DAD file in Table 1. It is obvious that the prediction error increases when the calibration samples and test set samples are analysed on different occasions.

In the analysis of the 15 samples on the three occasions, a single control sample containing 0.22 mg ml^{-1} lidocaine was included. Hence the lidocaine content of the control sample was in

Table 3
Prediction results of the samples in external test set A and the control sample on three different occasions with the DAD method (average spectrum whole DAD file)

Sample number	Accepted reference value (mg ml^{-1})	Predicted concentration (mg ml^{-1})		
		First occasion	Second occasion	Third occasion
1	0.153	0.158	0.159	0.153
2	0.166	0.167	0.173	0.167
3	0.175	0.179	0.182	0.177
4	0.186	0.191	0.191	0.187
5	0.198	0.203	0.204	0.200
6	0.205	0.208	0.212	0.207
7	0.216	0.220	0.221	0.215
8	0.227	0.230	0.229	0.225
9	0.238	0.240	0.237	0.234
10	0.246	0.252	0.246	0.248
11	0.256	0.262	0.256	0.257
12	0.269	0.273	0.269	0.269
13	0.276	0.285	0.277	0.276
14	0.286	0.294	0.291	0.282
15	0.296	0.303	0.300	0.297
Control	0.220	0.223	0.225	0.219
RMSEP		0.0052	0.0047	0.0021
RSEP (%)		2.23	1.96	0.85

the centre of the concentration interval covered by the calibration set and test set A (0.15–0.3 mg ml^{-1}).

From the predictions of this control sample on the three different occasions, it can be seen that it was predicted slightly high on the first two occasions, 0.223(+1.4% from the accepted reference value) and 0.225(+2.3%), and slightly low on the third occasion, 0.219(−0.5%). This might indicate that the predictions of the 15 test set samples on the first two occasions were also a bit high and that the predictions on the third occasion were a bit low.

The differences in % between the predicted and accepted reference values of the 15 samples on the three occasions were calculated and the results are shown in Fig. 3a. The control sample indicated that predictions for the first two occasions were slightly high. As can be seen in Fig. 3a, this also seems to be the case for the 15 test set samples. For the first occasion, all predictions are slightly high, ranging from 0.9 to 3.4% above the accepted reference value. For the second occasion, all predictions but four are higher than the accepted reference value and the difference in % from the accepted reference value is in the range 4.2 to −0.5%. For the third occasion, on the other hand, the prediction of the content of the control sample was slightly lower than the accepted reference value, −0.5%. In Fig. 3a it can be seen that for the third occasion the predictions are more evenly spread around the accepted reference value, with eight prediction values above and four below in the range +1.6 to −1.2%.

From the six repeated analyses of the control sample performed together with the analysis of the calibration samples the precision can be estimated. If the repeated measurements are assumed to be normally distributed, a confidence interval of the average of the predictions of the control sample (μ) can be calculated from the equation:

$$\mu = \bar{x} \pm t(\sqrt{n}/s), \tag{3}$$

where $\bar{x}$ is the average of the predictions of the content of the control samples, t is the t value at the significance level chosen (here 95%) with the appropriate number of degrees of freedom ($n-1$), n is the number of samples and s is the standard

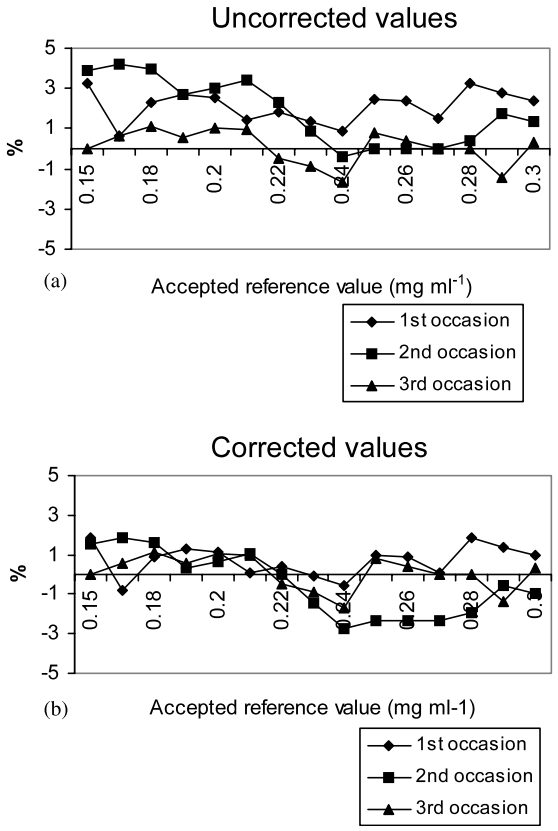

Fig. 3. Overview of the predictive results of the samples in external test set A on three occasions presented as difference from accepted reference value (%). (a) Without correction for the measured prediction error of the control sample, (b) with correction for the measured prediction error of the control sample if this was outside the confidence limits.

deviation. The confidence interval calculated for the average of the predictions of the control sample was $\mu = 0.220 \pm 0.0012$, giving the confidence limits 0.219–0.221 mg ml^{-1} for the sampling distribution of the mean.

If the prediction of the control sample on the three occasions is compared with the confidence limits calculated, it can be seen that on the first and second occasions the predictions are outside this interval (0.223 and 0.225), while being inside it on the third occasion (0.219). This indicates the presence of a systematic error on the first two occasions.

The predictions of the samples can be corrected according to the prediction error of the control sample analysed on that occasion. But this should only be done if the prediction of the control sample is outside the confidence limits. Hence corrections were made only for the first two occasions and not for the third, and the results obtained are shown in Fig. 3b. This simple correction seems to make the scatter of the prediction error more evenly spread around zero and hence lowers the overall prediction error (first occasion RMSEP 0.0024 and RSEP 1.02% and second occasion RMSEP 0.0039 and RSEP 1.70%).

Hence the use of a single control sample seems to give an indication of how reliable the predictions of the samples in the external test set are. Furthermore, correction of the measured predictions with the measured prediction error obtained for the control sample decreases the prediction error over the sample set and also decreases the systematic behaviour of the prediction error.

It is possible that more than one control sample would give better diagnostic information about the reliability of the predictions if a whole concentration interval were used, as in the calibration set and test set A. For instance, three control samples at the minimum, centre and maximum of the interval of the concentration interval would probably give better diagnostic information about the reliability of the predictions. However, in the case of the analysis of real samples from a pharmaceutical process, it is more likely that the aim is to analyse many samples containing the same amount of lidocaine. In this case, it may be enough to have one control sample having approximately the same content that the samples are expected to have.

In situations where the prediction of the control sample is outside the confidence limits, the decision about whether or not to correct the predictions of the samples could be further tested. If multiple analysis of the control sample is made on each occasion, the average of these predictions can be compared with the accepted reference value of the control sample with a significance test using t-statistics.

3.1. Practical considerations

In a previous investigation the practical procedure for an analysis of content and identity of lidocaine solutions with scanning UV–Vis spectroscopy and multivariate determination was outlined [6]. In this previous work soft independent modelling of class analogy (SIMCA) [14,15] was used for the determination of identity and PLS regression for the content determination. SIMCA classification is a powerful classification technique based on principal component analysis (PCA) or PLS, which uses the multivariate residuals of each sample for the classification. From the residuals of the samples in the calibration set, a confidence region for the calibration class is constructed around the principal component. New samples are regarded as members of the class if their distance from the principal component space does not exceed a critical limit defined by the confidence region. The results obtained in this way can be used to determine the identity of the sample. A positive identity would then imply that the sample has been predicted to belong to the calibrated class, while the opposite holds true for a negative identity of the sample. When a calibration model is made with PLS, SIMCA classification can also be carried out in addition using the residuals of each sample from the PLS regression. Hence the PLS calibration model can be used for determination of both content and identity. The identity determination was not applied in this study, however, although it can easily be implemented. If control samples, SIMCA classification and PLS regression are employed for the analysis of new samples with the DAD method, the practical procedure for determination of identity and content is described in Fig. 4. The calibration model and confidence interval for the prediction of the control sample are assumed to have been carried out beforehand. The analysis of the samples and the control sample with the DAD method has been performed and the spectra of the samples and the control sample are transferred in digitised form to the calibration software which contains the PLS calibration model.

Firstly, the identity and content of the samples and control sample are determined with the PLS calibration model (1). If the identity is negative, this indicates a significant difference between the samples analysed and the calibration model, making the content predictions unreliable. This can be caused by gross errors such as instrumental errors influencing the spectra or by contaminated samples etc. Hence if a negative identity is predicted for the samples or for the control sample, a reference method is needed for evaluation.

However, if the predicted identity of the control sample and the samples is positive, the spectra of the samples will then fit well into the multivariate calibration model and the predictions of the content can be regarded as reliable.

The estimated prediction error of the control sample can thereafter be used to detect any small systematic error in the predictions, which may justify making a correction to the predictions of the samples (2). To decide this, the confidence interval for the content of the control sample can be utilised as a specific limit for whether or not to make any correction. After this step the analysis of the samples is finished (3).

Multivariate calibration was used in this study even though the content of the lidocaine solutions could have been determined using univariate calibration. However, in order to determine the identity and to be able to use the same calibration model over time, a reliable method for identifying new samples is needed, and this can be achieved by the use of the multivariate residuals. Moreover, multivariate calibration using many variables is generally more robust in relation to instrumental variation and interference from other UV absorbing compounds than univariate calibration.

The procedure described in Fig. 4 could probably be easily automated and implemented with the help of computer software. In a previous study the term high capacity analysis (HCA) was introduced as an analytical approach consisting of spectroscopic analysis, chemometric data evaluation and a high level of automation [7]. The DAD method proposed, with some further development regarding automatic export of data and implementation of the practical procedures suggested in Fig. 4, could lead to an HCA method. This method could then serve as a fast and efficient analytical approach for screening purposes or industrial

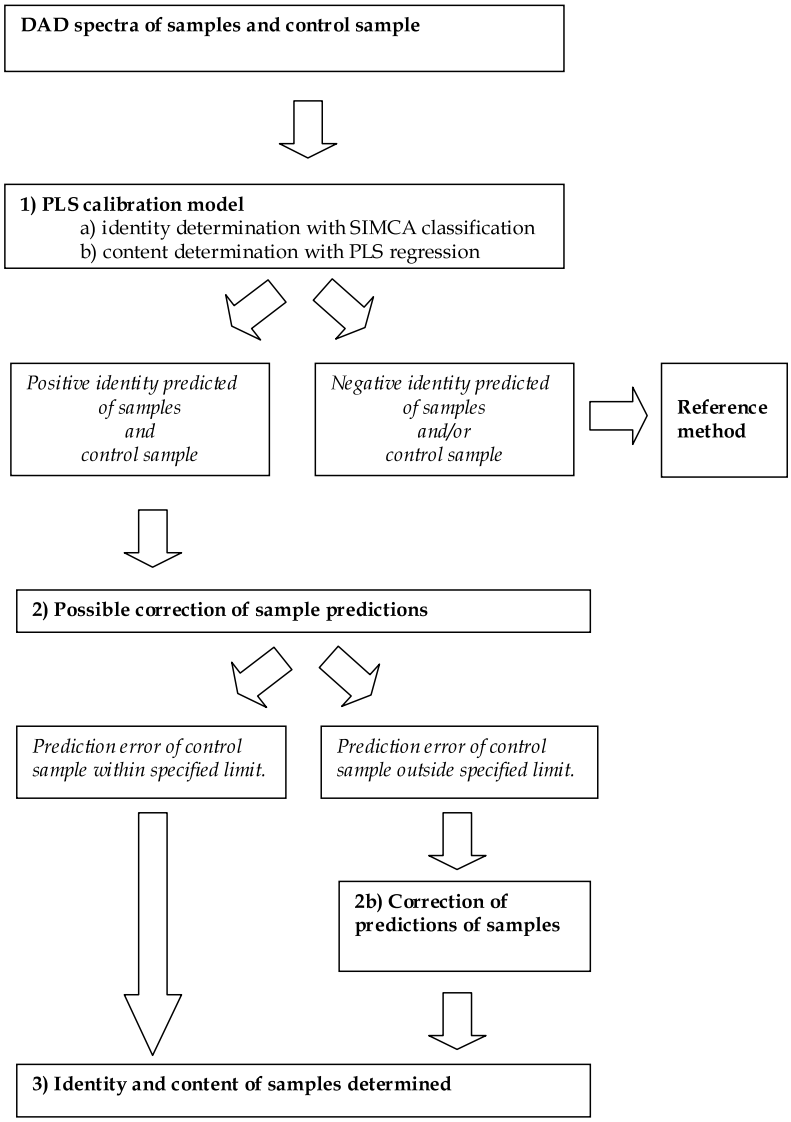

Fig. 4. Schematic diagram of the procedure for the identity and content determination with the DAD method using a control sample for estimation and correction of the prediction error.

quality control, where the same calibration model could be used over periods of time without the need for recalibration.

4. Conclusion

This study shows that the use of a control sample could be one way of diagnosing and estimating the prediction error as well as correcting the predictions, thereby lowering the prediction error. The ease of use, automation and high speed of the DAD method make it attractive for routine multivariate determination of pharmaceutical solutions. Finally, the practical procedure proposed could be a way of implementing the DAD method as a high-capacity analysis method for routine use.

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