Pergamon

0731-7085(95)01333-4

Journal of Pharmaceutical & Biomedical Analysis, Vol. 13, No. 4/5, pp. 419–423, 1995

0731-7085/95 $9.50 + 0.00

Quality control in manufacturing process by near infrared spectroscopy*

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Abstract: The combination of a pattern recognition technique with near infrared spectroscopy (NIR) to determine the conformity of a pharmaceutical mixture can be used in the routine checking of a pharmaceutical product. All the chemical and physical characteristics of the product that influence the NIR spectrum affect the qualification. The qualification is used to determine several deviations in the process: moisture, particle size and non-homogeneity. This work presents a method for the qualification analysis of a pharmaceutical mixture using the standard software of the instrument and a new program (DISPLOT). This program allows the acquisition of the plot of the scaled distances with its sign vs the wavelength.

Keywords: *Near infrared spectroscopy (NIR); qualification; C-PLOT; DISPLOPT; pharmaceutical; routine analysis; pattern recognition technique.*

Introduction

The pharmaceutical industry must guarantee the correct dosage, bioavailability and stability of drug products. Therefore, there must be exhaustive control over all materials and processes that contribute to their manufacture.

In order to monitor possible deviations in the preparation, it is advisable to carry out some tests during the different manufacturing stages. These tests can be: determination of content and homogeneity of the mixture, moisture, particle size, density, viscosity, etc. The analytical techniques used must be quick in order to minimize the downtime between the manufacturing process of the product.

Near infrared spectroscopy (NIR) has been proven to be a useful tool in different industrial fields [1–3]. Its use in pharmaceutical analysis is not yet widespread as a routine method, although several reviews have been published [4, 5] which included very diverse applications such as: the identification of raw materials [6–8], the determination of particle size [9–11], and the determination of one or several product components [12–14].

There are two basic procedures in the routine testing of a pharmaceutical product using NIR. The first one entails the determination of one or several components (quantitative analysis), using a suitable calibration based on the following algorithms: step-wise linear regression and partial least squares [14]. In order to carry out the calibration it is necessary to use production samples, but this has the disadvantage of having a very narrow range of concentration of analytes. A suggestion has been made [12] to increase the range of concentrations by using laboratory-prepared samples. The second procedure consists exclusively of determining whether the product is within the specification limits, that is to say, to identify any deviations in the process. This can be done by using certain supervised pattern recognition techniques (qualification). Qualification involves comparing the spectrum of the sample with the spectra of this product contained in the library, that correspond to samples which are within the specifications. The spectra of the samples included in the library are represented by a certain tolerance within the wavelength

*Presented at the Fifth International Symposium on Pharmaceutical and Biomedical Analysis, Stockholm, Sweden, September 1994.

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domain, that is due to the natural variability in the manufacturing process. The qualification process checks if the spectrum of the sample is enclosed wihtin this tolerance. The qualification is performed by computing the distance at each wavelength between the value of the sample and the average spectra of the library product. If the maximum distance computed does not surpass a preset threshold, the sample is qualified.

The NIR spectrum depends on the chemical and physical characteristics of the product all of which affect the qualification, whereas in quantitative analysis, only the parameters for which the calibration has been carried out are checked.

The NIR spectrum may change slightly due to small variations in the manufacuring process or in the characteristics of any of the raw materials. In this case it is necessary to check and adjust the calibration model with a new set of samples. If the modification is important then a new library must be prepared, being less laborious than to perform a new calibration for quantitative analysis of the different parameters.

For this reason we consider the use of the qualification for the product control to be a more practical option. It is only necessary to analyse the samples by the reference method in the case of obtaining a "fail" qualification which indicates that there is some deviation in the process. The reference analysis can provide information on the possible sources of deviation.

An alternative to the reference analysis is the Van der Vlies *et al.* [8] method based on a C-PLOT (plot of the absolute and scaled distance vs the wavelength). In several cases it is possible to correlate a deviation in the process to a pattern in the C-PLOT. It is therefore not necessary to use the reference analysis.

A visual inspection of C-PLOT may signal a deviation but without indicating if it is produced by an excess or a defect of some parameter.

This work presents a fast method for the analysis of a pharmaceutical mixture using a supervised pattern recognition technique (standard software of the instrument) which determined the higher absolute and scaled difference between the sample and the average spectrum at all wavelengths [15].

A program written in BASIC has been prepared that calculates (from the spectra transformed to the JCAMP format), the C-PLOT and the DISPLOT (Plot of the scaled distance with its sign versus the wavelength), using the equations

$$D_{A_i} = \frac{|X_i - \bar{X}_i|}{\sigma_i} \quad (1)$$

$$D_i = \frac{|X_i - \bar{X}_i|}{\sigma_i} \quad (2)$$

where D_{A_i} is the absolute distance and D_i is the distance with its sign at the wavelength i, X_i is the value of the magnitude of the spectrum (normally second derivative) corresponding to the wavelength i. $\bar{X}_i$ and σ_i are the mean and the standard deviation of all spectra which form the class (calibration) corresponding to the wavelength i.

In some cases the use of the DISPLOT allows the determination of the sign of the deviation produced.

Experimental

Sample

Mixture of a polyalcohol and a cellulose as the main components and a thickener as the minor component.

Instruments

NIRSystems 6500 Spectrophotometer, with Sample Transport module for sample presentation.

Software

The instrument is governed by the NSAS (Ver. 3.25) and IQ2 (Ver. 1.13) programs. In addition it is possible to carry out the necessary transformations for the spectra and the qualitative analysis of the sample. The program DISPLOT, written in QuickBasic v 4.5., is used to obtain the C-PLOT and the DISPLOT.

Results

Forty-five commercial batches which were qualified as AGREED by the Quality Control laboratory were used to define the limits of the variations to the NIR spectra of the product. The second derivative spectra in the wavelength range 1150–2300 nm were used. In Fig.

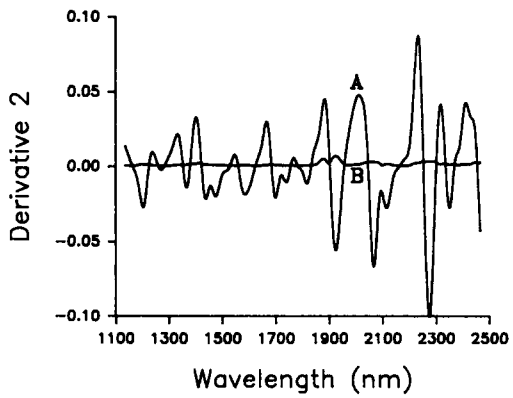

Figure 1
Average (A) and standard deviation (B) spectra of the samples included in the library.

1 the average and standard deviation spectra of the samples are shown.

The analysis of almost 80 different batches has been carried out. In the majority of cases, these samples are qualified as "agreed" using the standard software of instrument (the higher distance is lower than 3).

The C-PLOT and DISPLOT from the samples with "fail" qualification were obtained. These samples were classified into four groups according to the shape of the plot and the wavelength which presented the greatest distance from the mean.

The first group consisted of samples with a maximum distance at around 1950 nm. These high distances can be attributed to moisture which is well known to absorb strongly in this region of the spectrum. The reference analysis (Karl Fisher) was carried out and verified that these samples had moisture values which were either too high or too low. In Fig. 2 the C-PLOTs of two samples are shown. In Fig. 3 the DISPLOT of the same samples are shown. It can be seen that sample H035 has a deviation of the same sign as the spectrum, implying greater absorption in this part as indicated by the reference method. Conversely, sample H109 has deviations of the opposite sign to the average spectrum which indicates that this sample has less absorption (less moisture).

The second group of samples exhibit to large distances in different parts of the spectrum where there are important absorptions. This means that the deviation produced affects the whole spectrum, as well a physical parameter of the sample. The reference analysis confirms certain particle size deviations from normal. When the DISPLOT is obtained from these

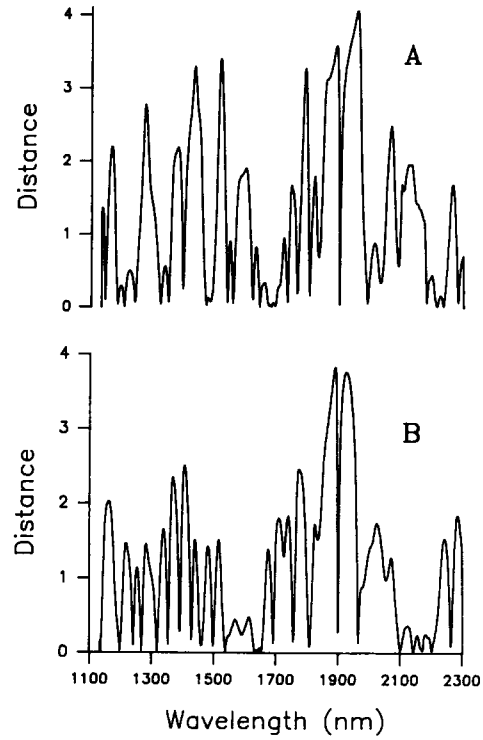

Figure 2
C-PLOT of the samples H035 (A) and H109 (B).

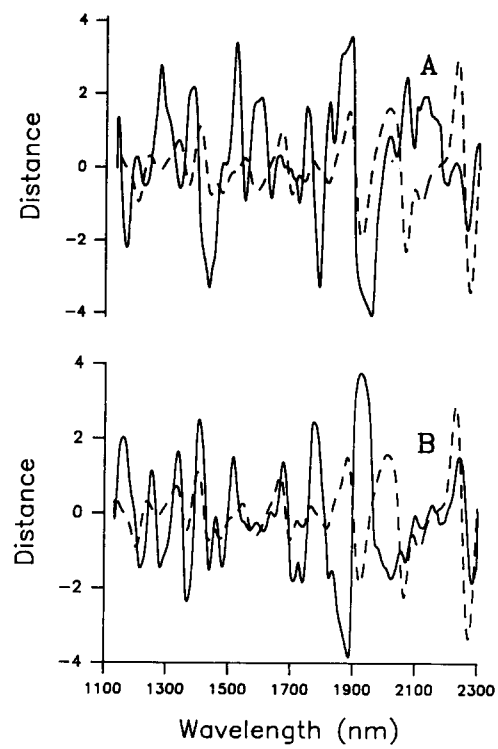

Figure 3
DISPLOT of the samples H035 (A) and H109 (B). The dashed line represents the average spectrum with an arbitrary scale but centered around zero.

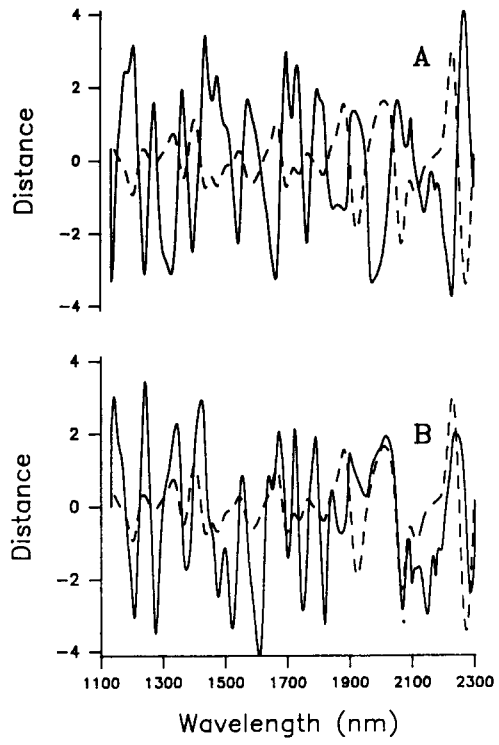

Figure 4
DISPLOT of the samples H098DM (A) and H003DS (B). The dashed line represents the average spectrum with an arbitrary scale but centered around zero.

samples, distances greater than 3 are observed in different parts of the spectrum and different wavelengths depending on the samples.

In Fig. 4 the DISPLOTs of sample H098DM (small particle size) and of sample H003DS (larger particle size) are shown. It is evident that in all maxima of the spectrum of the first sample, the distance is of the opposite sign to the average spectrum. This indicates that there is less absorption in the whole spectrum. On

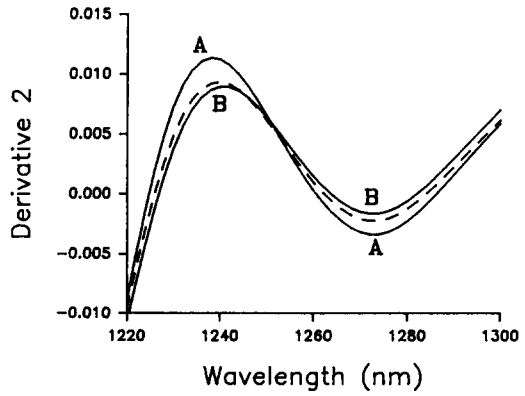

Figure 5
Average (dashed line) and spiked samples spectra. (A) with polyalcohol and (B) with cellulose.

Table 1
Values of higher distance in the interval 1200–1300 nm of the different bins of the batch H080 before and after batch homogenization

Batch H080	Before		After	
Bin	Distance	Wavelength	Distance	Wavelength
1	3.93	1276	0.87	1258
2	2.64	1276	2.94	1276
3	3.88	1276	2.22	1276
4	2.87	1276	1.63	1280
5	6.34	1276	0.90	1252
6	3.07	1276	2.45	1276
7	3.50	1276	2.31	1246
8	2.33	1276	1.58	1246
9	4.57	1276	1.42	1246

Table 2
Values of higher distance in the different bins of the batch H081 before and after changing the lamp

Batch H081	Before		After	
Bin	Distance	Wavelength	Distance	Wavelength
1	2.43	1158	3.57	1820
2	4.46	1820	2.93	1820
3	3.18	1150	3.27	1820
4	4.04	1820	2.93	1150
5	4.75	1820	3.27	1150
6	3.08	1478	2.41	1150
7	4.61	1820	2.87	1822
8	2.96	1276	2.35	1442
9	4.38	1820	2.31	1478

the other hand, in sample H003DS the value of the distances have the same sign as the average spectrum for most of the spectrum, this is in accordance with a larger particle size as is indicated by the reference analysis. However, around 1800 and 2000 nm this does not occur since, a low moisture content of this sample can explain this discrepancy.

The third group of samples with "fail" qualification have distance values greater than 3 between 1240 and 1280 nm. Spiked laboratory samples have proved that the deviation from these wavelengths is the result of a variation in the chemical composition of the sample. Fig. 5 shows two spiked samples with distances slightly greater to 3.

Table 1 shows the results obtained in the analysis of all bins of the same batch before and after homogenization. It is evident that the value of the higher distance in this part of the spectrum is greatly reduced after the homogenization process.

Finally, the last group is made up by samples with "fail" qualification, which do not have significant deviation according to the reference analysis. Obtaining the DISPLOT, the wavelength with the maximum distance corresponds to a zone of the spectrum where the signal is very weak. This means that small randomly distributed deviations may cause large distance values in zones of the spectrum where there are very small absorptions. One source of these deviations could be caused by instrumental noise. It is thus advisable to check thoroughly the state of the instrument (lamp, detectors, etc.) periodically and thus to reduce the "fail" qualification of a sample without deviations in the process.

Table 2 presents the results of the qualification of different bins of the same batch before and after changing the lamp. The distance of the majority of the bins was significantly reduced by reducing the instrumental noise.

Conclusions

The use of near infrared spectroscopy (NIR) combined with a pattern recognition technique is a useful and rapid tool for determining the quality of pharmaceutical products in an intermediate stage of the manufacturing process. The qualification, when using the whole spectrum, detects the majority of deviations that may occur in the process in a shorter time. The use of the DISPLOT allows the determination of the type and direction of the deviations produced.

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[Received for review 21 September 1994; revised manuscript received 21 November 1994]