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Multivariate control charts based on net analyte signal (NAS) for characterization of the polymorphic composition of Piroxicam using near infrared spectroscopy

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ABSTRACT

Near infrared spectroscopic and multivariate statistical control charts based on the net analyte signal (NAS) were applied to the polymorphic characterization of Piroxicam samples. Three different polymorphic forms (I, II and III) were studied, using X-ray powder diffraction (XRPD) and scanning electron microscopy as reference techniques. Samples containing form I were considered inside the quality specifications and forms II and III were impurities. Three control charts were developed: the NAS chart that corresponds to the analyte of interest (polymorphic form I), the interference chart that corresponds to the contribution of other compounds in the sample and the residual chart that corresponds to nonsystematic variation. From the limits estimated for each chart using samples inside the quality specifications, it was possible to identify samples that did not present polymorphic form I. The use of multivariate control charts provides a rapid evaluation of purity and the polymorphic composition of pharmaceutical formulations based on Piroxicam.

1. Introduction

Many pharmaceutical solids exhibit polymorphism, which is frequently defined as the ability of a substance to exist as two or more crystalline phases that have different arrangements and/or conformations of the molecules in the crystal lattice [1–3]. Thus, in the strictest sense, polymorphs are different crystalline forms of the same pure substance in which the molecules have different arrangements and/or different conformations of the molecules. As a result, polymorphic solids have different unit cells and hence display different physical properties, including those due to packing, and various thermodynamic, spectroscopic, interfacial, and mechanical properties [1–3].

Fundamentally the method used to give the structural information on a solid material is X-ray powder diffraction (XRPD) [4]. The X-ray technique, whether performed using single crystals or powdered solids, is concerned mainly with structural analysis and is therefore eminently suited for the characterization of polymorphs and solvates. An external examination of crystals reveals that they often contain facets, and that well-formed crystals are completely bound by flat surfaces. Planarity of this type is not commonly encountered in nature, and it was quickly deduced that the morphological characteristics of a crystal are inherent in its interior structure. In fact, the microscopic form of a crystal depends critically on structural arrangements at the atomic or molecular level; the underlying factor controlling crystal formation is the way in which atoms and molecules can pack together. A review of crystallography from the pharmaceutical viewpoint is available [5].

Infrared spectroscopy has been used for the polymorphic distinction of compounds and presents some advantages in relation to classical techniques for polymorphic analysis, since it is generally fast, cheaper, can be automated and can reduce the need for solvents and toxic reagents associated with wet chemical methods. Examples of

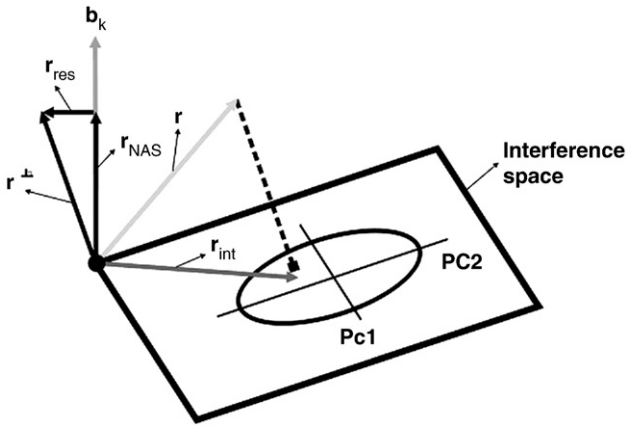

Fig. 1. Schematic overview of the separation of the spectrum **r** into three different contributions, the NAS values indicated by the vector $\mathbf{r}_{NAS}$, the composition of the excipients indicated by the vector $\mathbf{r}_{INT}$ in the interference space, and the residuals indicated by vector $\mathbf{r}_{res}$, perpendicular to of the regression vector NAS $\mathbf{b}_k$.

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Table 1
Data sets composition.

Sample set	Form I (%)	Form II (%)	Form III (%)	Excipient (%)
A	30–40	0	0	70–60
B	0	20–25	0	80–75
C	0	0	15–20	85–80
D	30–40	0	0	70–60

this application are diffuse reflectance infrared (DRIFT-IR), attenuated total reflection Fourier transform infrared (ATR-FTIR) and near infrared (NIR) [6–12].

Multivariate methods can help the analyst to extract the relevant qualitative or quantitative information from spectra, and these methods can help when deriving rapid methods for quality control [13–15]. In this sense, multivariate control charts have been used for quality monitoring using infrared spectroscopy [16,17]. The basis of this approach is to build an empirical model of a set of measurements obtained under normal operating conditions (NOC). Using this model, statistical confidence limits are calculated. New measurements are projected onto this model, and the statistics calculated should be within the confidence limits. Recently, new multivariate control charts based on the net analyte signal have been proposed to perform multivariate quality monitoring [18]. The advantage of these charts is that systematic variation in the product due to the analyte (or property) of interest is separated from the remaining systematic variation due to all other compounds in the matrix. This enhances the ability to flag products out of statistical control.

Piroxicam (4-hydroxy-2-methyl-*N*-(2-pyridyl) 2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide) is a nonsteroidal antiinflammatory and analgesic drug [19] that presents an interesting case of polymorphism. Three polymorphic forms (I, II and III) and one monohydrate form can be obtained by crystallization from saturated solutions in various solvents [20]. Since polymorphism can change the pharmacokinetic and pharmacodynamic characteristics of Piroxicam [21], it is important to develop quality control methodologies for the polymorphic determination of this drug.

The aims of this work were to build and to validate multivariate control charts based on the net analyte signal for quality monitoring of the polymorphic compositions of a pharmaceutical formulation based on Piroxicam using near infrared spectroscopy. For this purpose, firstly, a study using XRPD and microscopy was carried out to characterize the different forms of Piroxicam that crystallize under different conditions. Secondly, the multivariate control charts were developed and validated.

2. Theory

The basis for the development of the control charts is represented in Fig. 1 where a sample spectrum (vector **r**) is split into three different contributions: $\mathbf{r}_{NAS}$ (NAS vector), $\mathbf{r}_{INT}$ (interference vector) and $\mathbf{r}_{res}$ (residual vector):

$$\mathbf{r} = \mathbf{r}_{NAS} + \mathbf{r}_{INT} + \mathbf{r}_{RES} \tag{1}$$

The NAS vector corresponds to the analyte of interest [22]; all the remaining information not including the analyte is explained by the interference vector and the information that could not be explained by either NAS or the interference vectors will be in the residual vector. The subspace is called the interference space. Spectra of blank samples or spectra of the pure interferences can be used to span the interference space. The interference space can be found by applying principal component analysis (PCA) to mean-centered sets of blank (or interfering constituent) spectra:

$$\mathbf{R}_{-k} = \mathbf{P}\mathbf{T}^T + \mathbf{E} \tag{2}$$

where $\mathbf{R}_{-k}$ is the mean-centered spectra, **P** is the loadings that define the model for the interference space, **T** is the scores and **E** is a matrix of the residuals. Then the interference vector can be computed by projecting the vector **r** into the interference space:

$$\mathbf{r}_{INT} = \mathbf{P}\mathbf{P}^{+}\mathbf{r} \tag{3}$$

where $\mathbf{P}^{+}$ is the pseudo-inverse of the loading matrix.

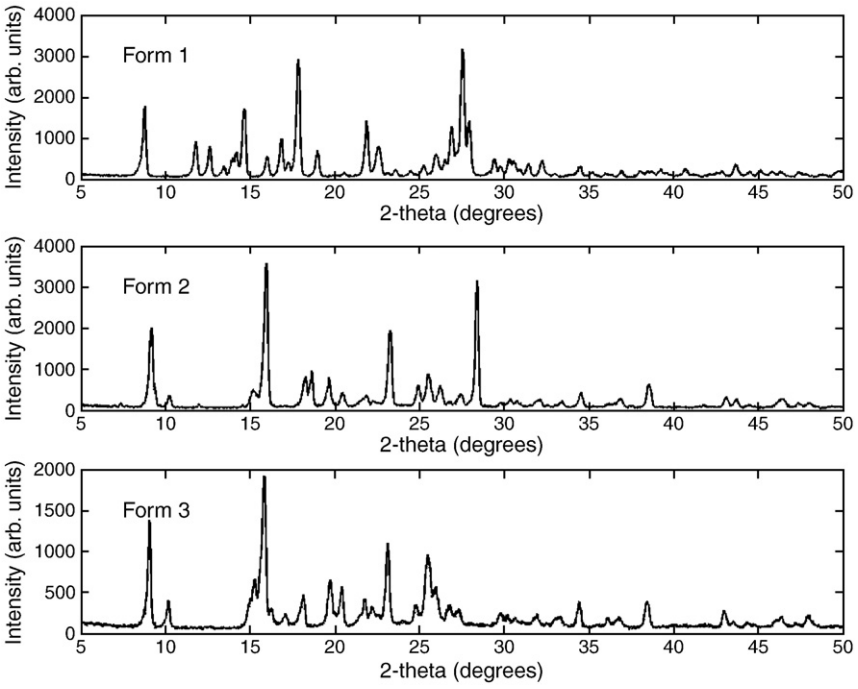

Fig. 2. Powder X-ray diffractograms of crystal forms of Piroxicam: (1) form I; (2) form II; and (3) form III.