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Multivariate control charts for monitoring captopril stability ☆

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ABSTRACT

Captopril, an antihypertensive drug, is seriously susceptible to oxidative degradation by high temperatures, humidity, and by the presence of hygroscopic excipients. The captopril disulfide is the main degradation product. In this study, multivariate control charts have been designed in order to monitor the captopril stability by using Hotelling's T^2 statistics and the Squared Prediction Error (SPE). The High-Performance Liquid Chromatography was the analytical technique used. T^2 and SPE charts performance depend on the pre-processing applied. The scaling methods, particularly the chromatograms weighting in the region of captopril disulfide, highlight the relevant chemical information and sensitize the charts for the detection of minor changes regarding the operating conditions. 52 chromatograms from different batches of captopril in normal operating conditions have been used on T^2 and SPE charts training stage. From 11 samples, seven within their shelf life and four after their expiration date have been used in the validation stage. A stability study has been performed by putting captopril samples in a 40 ± 2 °C temperature and $75 \pm 5\%$ relative humidity climatic chamber. Captopril samples have been removed weekly from the climatic chamber in the course of six months. A Principal Components Analysis has been performed in the data set and the scores of the first 3 components have been employed for the Hotelling's T^2 building, while the SPE chart has been designed with the model residuals. The multivariate control charts are sensitized to monitor chromatographic profile changes and captopril stability standard changes.

1. Introduction

The quality control of pharmaceutical production has been even more important in the recent years. The International Conference on Harmonisation (ICH) Q3 [1,2] guidance currently recommends a pharmaceutical products definition change. The focus of the quality control changed from purity in active pharmaceutical ingredients to impurity and degradation in finished pharmaceutical products [3]. Impurity and degradation product profiles in Active Pharmaceutical Ingredients (API) and drugs can be evaluated by stability tests.

Stability tests provide evidence on how the pharmaceutical product quality varies over time under the influence of environmental factors, such as temperature, humidity and light [4]. Monitoring the drug stability is one of the most effective methods for assessment, prevention and safety issues related to product quality during its shelf life. The drugs security can be assessed by monitoring the formation of degradation products which may generate decrease in the therapeutic efficacy and/or cause patient intoxication [5].

Multivariate Statistical Process Control (MSPC) is a methodology based on control charts used to monitor the multivariate process stability. The objective is to monitor the performance of a process over time in order to detect any special events that may occur. Typically, control charts based on Hotelling's T^2 statistic and the Square Prediction Error (SPE), also known as Q statistics, are employed for the detection of an out of control situation [6]. The multivariate control charts have been used to monitor and diagnose processes characterized by a large number of quality characteristics, which in turn have led to the application of multivariate projection methods as the Principal Components Analysis (PCA) [7].

The need to develop and apply analytical chemistry and chemometrics techniques to monitor impurities is currently quite evident in the pharmaceutical industry [8,9]. Chromatography is an analytical technique that adds extra information by directly relating failure origins with chemical composition changes, in particular in context of impurities or contaminants peaks. In addition, HPLC is widely available in pharmaceutical laboratories, once many reference methods and studies required for a drug production are achieved by this technique. Laursen and coworkers [10] have investigated the sensitivity of the MSPC based on PCA for monitoring, detection and diagnosis of small peaks of impurity embedded in drugs of high purity by analytical chromatography. The pharmaceutical products purity analysis based on HPLC generally deals with the number of peaks well known related target compound and impurity compounds [11].

Captopril is one of the most often consumed drugs in Brazil and is applied in the treatment of hypertension and congestive heart failure. Captopril is inexpensive and has a favorable effect on patient quality

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of life. Once hypertension treatment is usually for the entire life, these characteristics are important for the maintenance of treatment by the patient [12]. However, this drug is highly susceptible to oxidative degradation caused by high temperatures and humidity, and the hygroscopic excipients' presence. Its main impurity is the captopril disulfide which beyond the active principle degradation reduction in high quantities provides a tablet metallic taste and reduces the therapeutic adherence [13]. According to the United States Pharmacopeia (USP) [14] the disulfide captopril percentage in tablets should not exceed 3.0% m/m and the official method recommended for this impurity quantification is the High-Performance Liquid Chromatography (HPLC). Fig. 1 shows the captopril degradation reaction to form captopril disulfide.

In this work, we have used captopril samples produced by the Laboratório Farmacêutico do Estado de Pernambuco Governador Miguel Arraes (LAFEPE), in Recife, Brazil, in normal operation conditions and verified by the reference method to build multivariate control charts from the sample chromatograms. Then we have evaluated the charts by using tablet samples within their shelf life and after their expiration and finally verified the chart identity variations in the sample composition submitted to climatic chamber stability test which simulate extreme conditions which the drugs can be submitted to in warehouses or pharmacies shelves.

2. Theory

Hotelling's T^2 control chart is the commonly used procedure for a multivariate process monitoring and controlling. It is based on Mahalanobis distance for monitoring the average process vector which can be calculated for each sample i by the following equation [15]:

$$T_i^2 = (\mathbf{x}_i - \bar{\mathbf{x}})^T . \mathbf{S}^{-1} . (\mathbf{x}_i - \bar{\mathbf{x}}) \quad (1)$$

where $\bar{\mathbf{x}}$ is the average vector and $\mathbf{S}^{-1}$ is the inverse sample covariance matrix obtained from a statistical control historical data set. The relationships between the variables considered by the covariance matrix are used to measure the relative distance between a given p-dimensional $\mathbf{x}_i$ point and the average sample vector $\bar{\mathbf{x}}$ [16]. The T_i^2 value shall be compared to the Control Limit (CL) for concluding the process status: if T_i^2 is lower than CL then the process is "under control" in $\mathbf{x}_i$ point, and if T_i^2 is higher than CL, the process is declared "out of control" in $\mathbf{x}_i$ point. The control limit calculation will depend upon the process parameter estimation.

The multivariate charts analysis must be defined on two different stages with two different control limits [17]: In Phase I, the control charts are used to test retrospectively if the process was under control when the first observations were collected. Control Limits calculated upon an unstable process, or out of control, can be inaccurate and reduce the charts effectiveness on the next stage. Thus, a control limit for Phase I (CL^I) is calculated specifically to verify if the training samples are in control. Samples out of control in Phase I are purging of the training set as outliers. The control limit for individual observations on Phase I to the T^2 chart must be approximate by a beta distribution [18], and calculated by:

$$CL_{T^2}^{I} = \frac{(n-1)^2}{n} \beta_{1-\left(\frac{\alpha}{2}\right)\left(p/2,\frac{(n-p-1)}{2}\right)} \quad (2)$$

where $\beta_{1-\left(\frac{\alpha}{2}\right)\left(p/2,\frac{(n-p-1)}{2}\right)}$ is the percentile $100 \times (1-\alpha)$ of beta distribution with $p/2$ e $(n-p-1)/2$ degrees of freedom, n is the number of samples and p the number of variables.

In Phase II, the control charts are used to test if the process remains under control when future observations are monitored [19]. The control limit for Phase II (CL^{II}) is calculated in order to avoid false alarms. A new control limit is calculated only with training samples that were in control in Phase I. For Phase II, the new limit to be used is given by:

$$CL_{T^2}^{II} = \frac{p(n+1)(n-1)}{n(n-p)} F_{1-\alpha;p,n-p} \quad (3)$$

where $F_{1-\alpha;p,n-p}$ is the distribution percentile F with p and $n-p$ the degrees of freedom [17–19].

When the variable number is high, it is necessary to reduce it in order to avoid inconsistencies on $\mathbf{S}^{-1}$calculation. Principal Components Analysis (PCA) is the appropriate technique for this task. PCA consists in factor the data matrix according to the equation:

$$\mathbf{X} = \mathbf{TL} + \mathbf{E}, \quad (4)$$

where $\mathbf{X}$ is the data matrix, $\mathbf{T}$ is the scores matrix, $\mathbf{L}$ is the loading matrix and $\mathbf{E}$ is the residual matrix. In fact, only a few loadings vectors are necessary to modeling the major quantity of variance, thus we can make an effective dimensionality reduction. The residual matrix contains the variance that is not included in the model when the dimensionality reduction is made, and can be calculated by the equation:

$$\mathbf{E} = \mathbf{X} - = \mathbf{X} - \mathbf{T}_R\mathbf{L}_R \quad (5)$$

where R is the number of principal components (dimensions) retained in the model [20].

The use of PCA along with the multivariate control charts can improve the ability to detect initial failures and changes in the process in the structure of covariance of the variables [21]. The MSPC basis is collecting a historical data set when the process is working under normal operation conditions (NOC), performing a PCA with historical data for modeling and extracting the correlation structure of several variables correlated and using the modeled information in the multivariate charts control design [11].

The multivariate charts control based on PCA consists of two charts. The first one is the T^2 chart designed with the scores of PCA after the dimensionality reduction. This chart measures the distance of an observation into the center of NOC samples and determines if a specific sample has a systematic difference regarding the samples considered under statistical control. Thus it monitors the systematic variation included in the model.

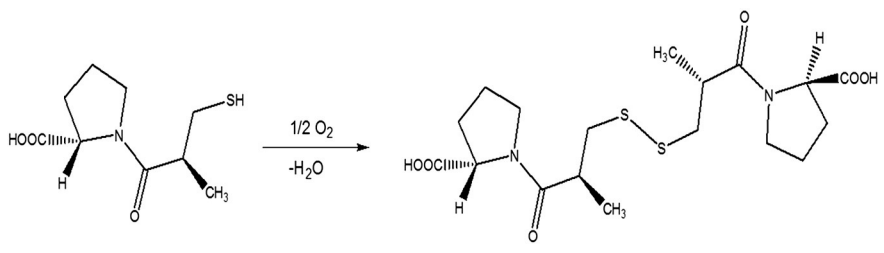

Fig. 1. Captopril degradation reaction in captopril disulfide.

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