PhD Thesis Abstract

Adoption of Chemometric and Instrumental Techniques for the Analysis of Drugs in Combinations

The thesis comprises four parts:

Part 1: Introduction to Chemometrics

This part comprises a brief idea about the definition and origin of chemometrics. It also presents the different topics of chemometrics like multivariate calibration, pattern recognition, signal processing, experimental design, multiway analysis, curve resolution methods, process control and others. This introduction gives examples for applications of chemometrics in the medical and pharmaceutical fields as well.

Part 2: Development and Validation of Stability Indicating HPLC and HPTLC Methods for Determination of Sulpiride and Mebeverine Hdrochloride in Combination

This part includes a general introduction about the chemistry and mode of action of sulpiride and mebeverine hydrochloride, followed by the presentation of the reported methods used for their quantitative determination. Experimental, results and discussion are also given.

This part comprises two sections:

Section A: A Stability Study for the Simultaneous Determination of Sulpiride and Mebeverine Hydrochloride by HPLC Hethod

In this section, mixtures of the sulpiride and mebeverine hydrochloride together with the reported interferants are separated on a reversed phase cyano column (5µm ps, 250mm x 4.6 id) using acetonitrile:water (70:30 v/v) adjusted to pH=7 as a mobile phase and metopimazine (MPZ) is used as

internal standard. The drugs were detected at 221 nm over a concentration range of 5 – 40 µg.ml^{-1} for sulpiride with mean percentage recovery = 99.75 ± 0.910 % and 5 – 60 µg.ml^{-1} for mebeverine hydrochloride with mean percentage recovery = 99.99 ± 0.450 %.

The selectivity of the proposed method was checked using laboratory prepared mixtures. The method was successfully applied to the analysis of the pharmaceutical formulation containing sulpiride and mebeverine hydrochloride with no interference from other dosage form additives. The percentage recoveries obtained were in accordance with those given by the reference method.

The validity and accuracy of the suggested procedure were further assessed by applying the standard addition technique.

The results of the proposed method were statistically compared with the reference HPLC method reported in the literature. The t and F values were found less than the tabulated figures indicating no significant difference with respect to accuracy and precision.

Section B: A Stability Study for the Simultaneous Determination of Sulpiride and Mebeverine Hydrochloride by HPTLC Method

In this section, both drugs are separated on an HPTLC plate coated with silica gel 60 F_{254} using absolute ethanol: methylene chloride: triethyl amine (7: 3: 0.2 by volume) as a mobile phase and scanning of the separated bands at 221 nm over a concentration range of 0.4 – 1.4 µg.band^{-1} for sulpiride with mean percentage recovery 101.01 ± 1.991 % and 0.2 – 1.6 µg.band^{-1} for mebeverine hydrochloride with mean percentage recovery 100.40 ± 1.868 %.

The selectivity of the proposed method was checked using laboratory prepared mixtures. The method was successfully applied to the analysis of the pharmaceutical formulation containing sulpiride and mebeverine hydrochloride with no interference from other dosage form additives. The percentage recoveries obtained were in accordance with those given by the reference method.

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Part 3: Partial Least Squares Regression, Spectral Residual Augmented Classical Least Squares and Support Vector Regression: A Comparative Study for Analysis of Colona® Tablets

Partial least squares regression (PLSR), spectral residual augmented classical least squares (SRACLS) and support vector regression (SVR) are amongst the best multivariate regression methods used recently for pharmaceutical analysis, although each of them has its unique performance.

The work introduced in this part aims to compare these three different chemometric methods, showing the underlying algorithm for each and making a modest comparison amongst them to indicate the merits and demerits of each. It also helps to highlight the importance of considering robustness and ruggedness of chemometric techniques for real life routine analysis, where recalibration is not usually easy to perform, while robustifiability of certain models could make it supersede other advanced models from the point of view of industry.

To project the comparison in a sensible way, the three methods are used for the stability indicating quantitative analysis of mixtures of mebeverine hydrochloride and sulpiride in binary mixtures and in presence of their reported impurities and degradation products (summing up to 6 components) whether in raw materials or in pharmaceutical tablets via handling the UV spectral data. All the mixtures were recorded at 226-320 nm.

For proper analysis, a 6 factor 5 level experimental design was established resulting in a training set of 25 mixtures containing different ratios of the interfering species. A test set consisting of 5 mixtures was used to validate the prediction ability of the suggested models. The proposed methods were

successfully applied to the analysis of pharmaceutical tablets containing mebeverine hydrochloride and sulpiride mixtures.

The methods indicate the ability of the mentioned multivariate calibration models to deconvolute the highly overlapped UV spectra of the 6 components' mixtures and to show prediction ability that is equivalent to the hyphenated precise separation techniques like HPLC, yet using cheap and easy to handle instruments like the UV spectrophotometer. This opens the scope for easier analysis of pharmaceutical products with higher numbers of interfering components (4 and more) without the need for experience, long time and expensive complicated instruments as the case with HPLC.

The results of the proposed methods were statistically compared with the reference HPLC method reported in the literature. The t and F values were found to be less than the tabulated figures indicating no significant difference with respect to accuracy and precision (except for the SRACLS method).

Part 4: On-line HPLC for Process Monitoring: Exploratory Analysis of Campaign 1, Process GW'553, CDI Stage

GlaxoSmithKline (GSK) is an international leading company in production of pharmaceutically active ingredients and pharmaceutical dosage forms.

The data handled in this chapter are obtained through collaboration between GSK (Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY, UK) and the Centre for Chemometrics (University of Bristol, UK).

In this project, GSK is trying to develop methods for online monitoring of impurities during the process of production of one of the active pharmaceuticals. In the presented work we are concerned with the analysis of what is called "The CDI stage" as one of the stages of the process called "GW'553". 608 chromatograms were provided after 4 days of continuous process, where the aim of the analysis is to find out which of these 608 chromatograms are not conforming to the steady state criteria, besides finding out the reason behind the abnormality by comparing it to the parallel log book and process variables information reported by the process analyst. Signal processing methods like baseline correction, peak alignment, peak detection

and integration, and peak matching were applied for proper handling of the chromatograms, then Principal Components Analysis (PCA) of the peak table data was performed coupled with implementing multivariate statistical process control charts (Q and D statistics) for finding out the outliers and determining whether they originate from systematic or non-systematic deviation reasons like the chromatographic changes and process variables changes respectively.

Keywords

Mebeverine hydrochloride, sulpiride, HPLC, HPTLC, stability indicating assay, chemometrics, PLSR, SRACLS, SVR, multivariate statistical process control, D and Q charts.

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