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Short communication

Integrating 2D correlation spectroscopy and discriminant analysis in analytical control laboratories

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Introduction

The increasing complexity of pharmaceutical systems and growing regulatory requirements demand advanced analytical methodologies capable of delivering high sensitivity, selectivity, and reliability. Conventional analytical techniques such as HPLC and UV/Vis remain essential tools in quality control laboratories; however, they often face limitations when dealing with highly complex matrices, overlapping spectral features, and subtle physicochemical changes (Kogawa et al., 2019).

Atorvastatin calcium trihydrate was selected for application as a representative pharmaceutical raw material due to its polymorphic behavior and relevance in quality control (Kogawa et al., 2019; Noda, 2022).

Two-dimensional correlation spectroscopy (2D COS) has emerged as a powerful extension of traditional spectroscopic techniques, enabling enhanced spectral resolution and deeper insight into molecular interactions and structural dynamics. [1] In particular, the two-trace two-dimensional (2T2D) correlation method enables direct comparison of two spectral datasets from different conditions, samples, or spectral regions (Silva et al., 2015).

In parallel, multivariate statistical techniques such as discriminant analysis provide robust tools for classification, pattern recognition, and differentiation of samples based on spectral features.

The integration of 2D correlation spectroscopy with discriminant analysis represents a promising analytical strategy, combining advanced spectral interpretation with statistical decision-making.

Materials and methods

Spectroscopic and X-ray diffraction analysis

Spectral data were obtained using vibrational spectroscopic techniques, primarily FTIR spectroscopy operated in ATR mode on a Perkin-Elmer system 2000 FTIR, over the range from room temperature to 200 °C, with an increment of 5 °C using a temperature-controlled cell (Silva et al., 2015). X-ray diffraction data were collected on an Ultima IV X-ray diffractometer (Rigaku Co.) using CuK_α radiation, operating in the θ–2θ scanning mode with a step-scan size of $\Delta(2\theta) = 0.02$ °.

Two-dimensional correlation spectroscopy (2D COS and 2T2D)

Two-dimensional correlation spectroscopy is based on mathematical transformation of spectral datasets collected under an external perturbation. The technique generates:

- Synchronous spectra, representing simultaneous changes in spectral intensities

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- Asynchronous spectra, revealing sequential or phase-delayed changes

The collected data were processed and visualized using Origin Lab software to enable interpretation of one- and two-dimensional spectral changes and temperature-induced molecular interactions.

Discriminant analysis

Discriminant analysis is proposed as a future statistical step to be applied to processed spectroscopic and X-ray diffraction data and/or 2T2D correlation maps. Extracted spectral and XRD features may be used to classify samples into predefined groups based on their spectral and structural characteristics. This approach could support differentiation between materials or batches, identification of deviations from expected profiles, and decision-making in quality control.

Results and Discussion

The application of generalized two-dimensional correlation spectroscopy to the obtained temperature -dependent ATR-FTIR spectra enabled detailed characterization of atorvastatin calcium structural dynamics. Moving-window 2D correlation analysis identified key thermal events, including water loss at approximately 85, 115, and 140 °C, as well as a dominant transition around 155 °C corresponding to the melting process. An additional low-temperature correlation response around 40 °C was also observed, suggesting that subtle spectral changes occur before the major dehydration events.

The synchronous perturbation-correlation moving-window correlation spectra showed that the critical thermal points were associated with a decrease in IR band intensities, supporting their assignment to the loss of molecules incorporated in the crystal structure, particularly crystal water. The generalized synchronous and asynchronous correlation maps enabled assignment of changes in O–H, N–H, C=O, C–C, and related vibrational modes. In particular, the correlation behavior of the bands around 3420 and 3210 cm^{-1} indicated that changes in O–H vibrations of crystal water precede changes in secondary amide N–H stretching vibrations. These findings support the interpretation that dehydration processes occur before major structural changes in the organic part of the molecule.

The extracted 2T2D and GEN-2DCOS spectral features provide a suitable basis for future discriminant-analysis models aimed at classifying pharmaceutical raw materials according to thermal behavior, structural state, and deviation from expected quality profiles.

Conclusion

In complex systems such as pharmaceutical raw materials or formulations, this approach offers significant advantages in detecting early-stage polymorphic transitions, degradation processes, and interactions between components, supporting improved product consistency and regulatory compliance. Integration of 2T2D correlation spectroscopy and discriminant analysis is expected to improve the detection and interpretation of complex pharmaceutical systems by combining advanced spectral resolution with statistical classification. The proposed framework remains adaptable and can be extended to different spectroscopic (IR, NIR, Raman) and structural (XRD) techniques within a wide range of pharmaceutical applications. Further research will focus on expanding the experimental dataset and quantitatively assessing classification performance under controlled laboratory conditions.

References

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