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Short communication

PCA-based chemometric screening of pharmaceutical packaging extractables using UV spectrophotometry

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Introduction

The increasing regulatory focus on extractables and leachables (E&L) from pharmaceutical packaging materials has highlighted the need for rapid analytical approaches for early migration assessment. The emerging ICH Q3E guideline (ICH, 2025) introduces a harmonized risk-based framework for evaluation of packaging-related extractables and their potential impact on medicinal product quality and safety.

Pharmaceutical packaging systems may release extractable compounds under normal or stress conditions depending on material composition, barrier properties, and manufacturing-related factors. Since comprehensive E&L characterization using advanced analytical techniques may be time-consuming and resource-intensive, chemometric analysis of spectrophotometric data could represent a useful preliminary screening strategy for comparative evaluation and sample prioritization.

Therefore, the aim of this study was to evaluate the applicability of PCA-based chemometric analysis of UV spectrophotometric data for classification of pharmaceutical packaging extracts according to migration-related chemometric behavior.

Materials and methods

Materials

Ethanol (96%, *V/V*) and distilled water were used to prepare the extraction solvent. The study included 20 extracts prepared from different pharmaceutical primary packaging systems, including conventional and multilayer blister systems, polyolefin packaging materials, glass containers, elastomeric closures, and aluminum-containing packaging systems.

Extraction procedure

Extract preparation was performed according to the general principles of USP <1663> (USP, 2020). An ethanol/water mixture (50:50, *V/V*) was used as extraction solvent to enable extraction of compounds with different polarity profiles while maintaining compatibility with UV spectrophotometric analysis.

Two extraction conditions were investigated: (i) room temperature extraction at 25 °C for 24 h and (ii) accelerated extraction at 60 °C for 4 h using a SONIC 12GT Ultrasonic Cleaner (Sonic, Niš, Serbia). Following extraction, all samples were filtered through blue ribbon filter paper prior to analysis.

UV spectrophotometric and chemometric analysis

UV absorbance measurements were performed at 220, 240, 260, 280, 300, and 320 nm using an Agilent 8453 UV–Visible Spectroscopy System (Agilent Technologies, USA) operated with Chem Station software. Principal Component Analysis (PCA) and chemometric data processing were

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performed using Orange Data Mining software (version 3.4; Orange Data Mining, 2026).

A semi-quantitative PCA-derived chemometric score was calculated using normalized PC1 and PC2 values weighted according to their relative explained variance contribution (90% and 10%, respectively).

$$\text{Chemometric score} = (0.90 \times \text{PC1norm} + 0.10 \times \text{PC2norm}) \times 100.$$

This approach is consistent with PCA-based composite index construction and multivariate scoring approaches (Praus et al., 2019).

Results and discussion

Principal Component Analysis (PCA) of UV spectrophotometric data obtained under room temperature conditions demonstrated distinguishable clustering patterns among pharmaceutical packaging extracts. Initial PCA analysis based on packaging type did not produce clearly separated clusters, likely due to the heterogeneous and multilayer composition of the investigated systems.

Therefore, samples were classified into four groups according to material composition, barrier properties, and relative leaching behavior. Lower-variability systems, including polypropylene (PP), high-density polyethylene (HDPE), and selected polyvinyl chloride/ polyvinylidene chloride/ aluminum (PVC/PVdC/Al)-based packaging materials, formed compact low-variance clusters characterized by lower PC1 and PC2 values, consistent with reduced extractable variability. Controlled PVC/PVdC systems formed an intermediate cluster with moderate dispersion, potentially associated with the presence of plasticizer-containing polymer systems.

Polyolefin and multilayer systems, particularly low-density polyethylene (LDPE)-containing packaging materials and aluminum/polyethylene (Al/PE) laminates, demonstrated increased PCA dispersion and greater chemometric variability. Glass and elastomer-containing systems demonstrated distinct PCA patterns.

Under accelerated extraction conditions (60 °C, 4 h), PCA cluster separation became less pronounced due to enhanced diffusion and migration processes, resulting in partially overlapping profiles.

A semi-quantitative chemometric score based on normalized PCA values was additionally calculated to support comparative sample prioritization. Higher chemometric scores reflected increased spectral variability and extractable-related dispersion. Clustering patterns were influenced more strongly by material composition and barrier properties than by packaging type alone.

Conclusion

The PCA-based chemometric analysis of UV spectrophotometric data represents a useful preliminary screening approach for comparative evaluation of pharmaceutical packaging extractables. The proposed exploratory classification approach enabled differentiation of packaging materials according to their barrier properties and relative extractable variability, reflected through distinct PCA distribution patterns.

Elevated temperature conditions reduced cluster discrimination, indicating enhanced diffusion and migration processes across different packaging systems. This approach provides a basis for development of an analytical tool for rapid and cost-effective screening of pharmaceutical packaging and early risk evaluation of packaging systems with potential to release extractables that may affect the quality of the medicines.

In the context of the emerging ICH Q3E guideline (ICH, 2025), preliminary chemometric screening may support selection of samples requiring detailed E&L characterization.

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