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Short communication

FT-NIR as a technique for objective measurement of film quality parameters

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Introduction

Film-coating is a widely employed technological process in the pharmaceutical industry used to enhance appearance, patient acceptability, stability, and swallowability. Titanium dioxide (TiO_2), an opacifying agent, has been re-evaluated by the regulatory agencies in Europe due to concerns over its potential genotoxic effects. Although the European Medicines Agency (EMA) has temporarily maintained TiO_2 inclusion in the list of approved colors for medicines, its use will be reassessed latest by February 2025 and pharmaceutical companies are encouraged to seek alternatives. TiO_2's unique properties make finding alternatives difficult. Iron oxides are possible substitutes for TiO_2 due to their high refractive indices, good opacifying power, as well as range of colors possible by their combinations (Blundell et al., 2022). To ensure the film-coated tablets have acceptable appearance, a critical quality attribute, optimization of the film-coating process is necessary. The intrinsic subjectivity of visual assessment can be substantially mitigated through the use of quantitative measurements during the coating process. This approach eliminates perceptual variations, fosters data-driven decision making, and assures a uniform quality, which is particularly challenging when coating with TiO_2 free films. Furthermore, orangish hues such as those obtained with the film used in the study have been shown to have the largest lightness and chroma appearance changes under different illuminants, making objective color identification especially important for consistent color quality. Studies have found complex dependencies of perceived saturation and lightness on the physical properties of surfaces, such as hue, relief height and specular roughness (Isherwood et al., 2021). Leveraging chemometric tools to analyze and calibrate spectral information, NIR spectroscopy's dual-dependence on a sample's chemical and physical attributes allows for precise determination of properties such as film thickness, surface roughness, porosity, tablet coating uniformity, which are properties that can be correlated with both tablet appearance and weight gain (WG). In this study, we utilized a chemometric approach using multivariate methods to analyze and correlate NIR spectral data with CIELAB values and weight gain obtained with a digital microscope camera and digital scale respectively, at different points during the coating process. The objective was to assess NIR spectroscopy's potential for monitoring weight gain and appearance in industrial-scale tablet coating processes.

Materials and methods

Tablet cores and coating materials: Biconvex tablet cores (diameter: 8 mm; mass: 200 mg ± 5.0%; Alkaloid-AD, Skopje), coated with an aqueous partially hydrolyzed PVA film coating (Opadry TF; Colorcon Inc, UK), containing talc, PEG 3350 and iron oxides yellow, red. Coating process: Tablets were coated in a partially perforated pan coater (Glatt GMPC, x2 spray nozzle, Glatt GmbH, Binzen, Germany). Samples were collected at 3.6 L, 4.0 L, 4.3 L, 4.0 L coating levels. Four tablets from each coating level were analyzed from both sides. Reference measurements: Weight gain of the tablets was measured using Sartorius Signum 1 electronic scale (Sartorius,

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Goettingen, Germany; used as an indirect way to infer film thickness). NIR measurements and analysis: Samples were measured using an Antaris II FT-NIR analyzer (4000 cm-1 to 10 000 cm-1; OMNIC; Thermo Fisher Scientific, US; SabIR fiber optic diffuse reflectance probe). Spectra visualization: Spectragryph 1.2. Color data: Images were taken with a portable microscope (MicroCapture Pro). CIELAB values were extracted using Fiji/ImageJ 2.9.0. Multivariate analysis: SIMCA 14.1 (Umetrics, Sweden).

Results and discussion

In our study, we found that substituting TiO_2 with iron oxides as the sole colorants to achieve satisfactory film coating appearance is a feasible strategy. This change necessitated process modifications, including a higher 5.5% weight gain, in order to minimize tablet and tablet-to-tablet color variations of tablets. Given potential dissolution related effects from higher film weight, optimal appearance requires precise control and thorough understanding of the coating process. NIR spectroscopy has the potential to be a non-destructive, reliable, and rapid method for the objective classification of film-coated tablets. FT-NIR reflectance spectra from both tablet sides suggest the log 1/R axis (Y axis) is responsive to film coating progression, with the peak shapes closely mirroring the NIR spectra of the Opadry film. The spectra at different stages of the film coating process overlap nearly completely, considering the Y axis offset, and peaks at 7180 cm-1, 7152 cm-1 and 4327 cm-1 are distinctive and absent in spectra of tablet cores or API alone. Multiple models (PLS) were built using the collected NIR spectra as X matrix, weight gain (WG) and CIELAB values for color (C) analysis (skewness and kurtosis of the lightness channel; L skew, L kurt) as Y variables (target parameters; TP) (Table 1). The model was tested for correlation of both weight gain and color, in order to evaluate NIR's ability to provide colorimetric and weight gain data from one spectral image. An improvement in the model parameters was observed by excluding the spectral data with a VIP score below 1 (9400-9250 cm-1; 8600-8000 cm-1; 7300cm-1-5900cm-1). Improved model quality was observed when DModX plot was used to exclude outliers. The PLS models had 4, 2, 5 LVs (latent variables) significantly contributing to the WG, C and combined WG+C models respectively. The model with weight gain was able to cluster samples effectively. When L skew and L kurt were used as the Y variables, a score plot of the first principal component clearly distinguished the 3.6L and 4.0L coating level and 4.3L and 4.7L coating level. Further, there was a negative correlation with a decrease in the skewness and kurtosis of lightness with progression in the film coating process, indicating a better tablet-to-tablet coating uniformity (Fig. 1). Moreover, the variation in scores between different sides of the tablet tended to decrease with increasing weight gain (Fig. 1), potentially indicating better coating uniformity with increased coating level, corresponding to perceived differences (WG+C, C models).

Table 1. Results of PLS calibration models

TP	RMSEE	RMSEcv	R2X	R2Y	Q2
WG	1.70 mg*	1.78 mg*	0.996	0.879	0.832
C	0.32** 1.29***	0.40** 1.40***	0.996	0.614	0.325
WG+C	0.33** 1.55 mg* 1.33***	0.42** 1.77 mg* 1.45***	0.998	0.742	0.533

*WG acceptance criteria (AC) - 212 mg ± 10.6 mg; **L skew low to high -0.283 to 1.181; ***L kurt low to high 0.971 to 11.653

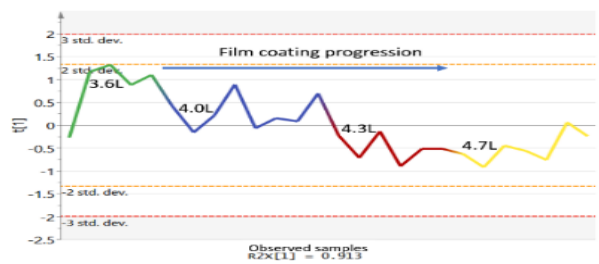

Figure 1. PLS score plot of PC1 indicating coating progression WG+C model

Conclusion

NIR spectroscopy can be applied for the determination of the quality of TiO_2 free film-coated tablets. Both progression of the film coating process and tablet coating uniformity could be distinguished by this preliminary model. Further work, utilizing an expanded dataset would be useful for building and validating a quantitative model for the determination of the end point of a film coating process with multivariate techniques which combine film thickness, colorimetric, and spectral data, potentially allowing for convenient in-line, real time monitoring.

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