Hyperspectral Imaging to Monitor Coat Thickness Uniformity in the Manufacture of Transdermal Drug Delivery Systems
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Purpose
Transdermal coat thickness is one of the critical in-process control parameters in the manufacture of transdermal drug delivery systems (TDDS). The uniformity in coat thickness determines the amount of drug loading in the formulation. Any non-uniformity in the coat thickness leads to deviation of drug load from target, which in turn impacts the in vivo drug delivery rate. Hyperspectral Imaging using near infrared spectroscopy (NIRS) is a potential technology that integrates spectroscopy and conventional imaging to obtain both spectral and spatial information of a material while it is in motion. Objective is to develop and validate the use of Near Infrared (NIR) hyperspectral imaging for its ability to monitor coat thickness uniformity of TDDS.

Methods
A placebo TDDS was formulated in-house with a mixture of acrylic and silicone adhesives (DuroTak® 87-900A:BIO-PSA® 7-4502 = 20:80) along with other excipients (e.g., oleyl alcohol, dipropylene glycol and polyvinyl pyrrolidone) and optimized for desired skin adhesion based on Chu criteria of viscoelastic properties. The TDDS were prepared for varying wet coat thickness (100-500 μm) with at least 6 TDDS sheets per thickness. The release liner (Fluoropolymer coated Polyester film, Scotchpak™ 1022 with a thickness of 76.2 μm) sheet (30 cm X 35 cm) was used as substrate for coating adhesive formulation and subsequent drying (Mathis LabCoater/Dryer LTE-S). The coated sheet (20 cm X 25 cm) was laminated with a backing membrane (Polyolefin Monolayer film, CoTran™ 9722 with a thickness of 76.2 μm), and packaged in a pouch until used for the study. Ten circular samples of 2.5 cm in diameter were cut from each of the TDDS. The dry coat thickness of the samples was measured using a digital micrometer. Images were acquired for all the samples with a Hyperspectral Imaging system equipped with a full range (1000-2500 nm) short wavelength infrared (SWIR) camera. The samples were divided into training and test sets to develop and validate the prediction model for coat thickness. The images were corrected with the calibrated dark and white references. The multiplicative and additive effects as well as baseline differences between the spectra were eliminated by normalizing using mean-centering and standard normal variate (SNV) correction. The processed images were subjected to chemometric analysis in order to qualitatively classify the TDDS samples as per the coat thickness utilizing a principle component analysis (PCA) model and then develop a partial least square (PLS) model to quantitatively predict the coat thickness. The feasibility of hyperspectral imaging as a real-time process analytical (PAT) tool for continuous monitoring of coat thickness was also investigated.

Results
The dry coat thickness of the training and test samples including the release liner and backing membrane ranged from 169.4±1.8 to 358.7±2.3 μm for a wet coat thickness of 100 to 500 μm as measured by the digital micrometer. The signal intensity of NIR spectra increased with increase in coat thickness. A scatter 2D density plot of PCA model classified the sample data into different clusters according to sample coat thickness. A tighter packing of the cluster indicated the coat thickness uniformity within each sample. Three principle components were sufficient to explain more than 90% of the variation in samples and to classify them according to their spectral intensity. A PLS model was developed and validated to predict coat thickness of a TDDS. The goodness of PLS model fit and goodness of prediction are 0.9933 and 0.9933 indicating an excellent fit to the training data and also good predictability. The % Prediction Error (%PE) for internal and external validation samples was less than 1 indicating the accuracy of the PLS model developed in the present study. When the PLS model was applied to detect the deliberate variation in coat thickness, it was able to predict both the small and large variations as well as identify coating defects such as non-uniform regions and presence of air bubbles.

Conclusion
Hyperspectral imaging appears to be an excellent non-destructive in-process analytical tool to monitor coat thickness uniformity for manufacturing TDDS.

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