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Evaluation of API-Distribution and Coating Thickness by NIR Spectroscopy and Raman Chemical Mapping

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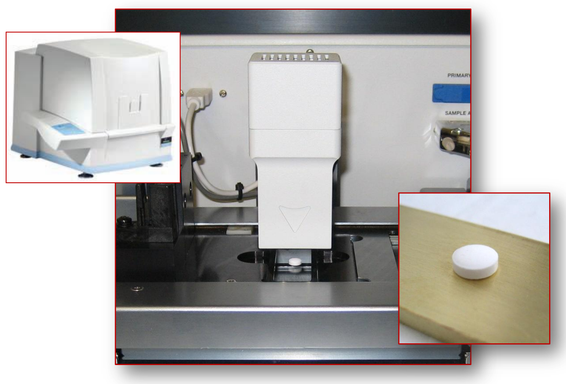
Introduction

Spray coating is an important unit operation in the pharmaceutical industry. The ultimate goal is to produce uniformly coated products with the desired amount of coating material, to guarantee controlled active pharmaceutical ingredient (API) release. The coating thickness and homogeneity can be determined with spectroscopic process analytical technology (PAT) tools, like near-infrared (NIR) and Raman spectroscopy. Here, both spectroscopic techniques were applied for the analysis and characterization of tablet coatings. Due to the relatively small coating thickness with respect to the penetration depth of the excitation, both laser light and Raman scattering penetrate through the coated layer. Hence, Raman chemical mapping can also be used to analyze qualitatively the chemical composition (i.e. the distribution of (active) components) in tablets. A quantitative multivariate data analysis (MVDA) based model for the tablet coating thickness was developed on basis of tablets sampled from different stages of a coating process [1,2].

Methods

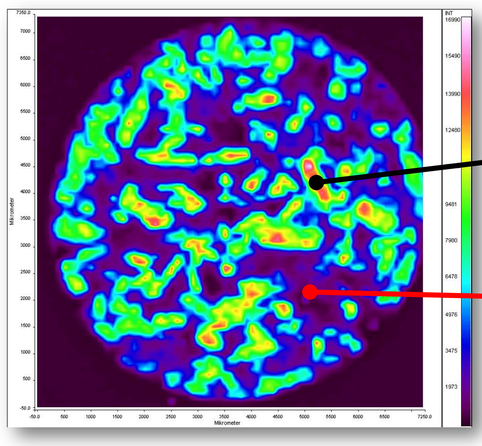
Raman Spectroscopy and Imaging

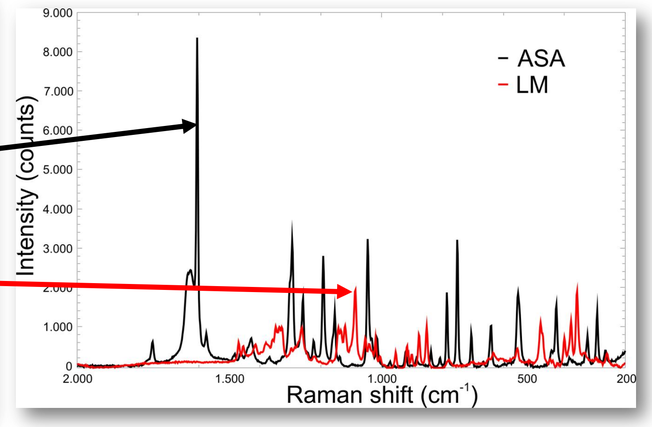


Near-infrared Spectroscopy

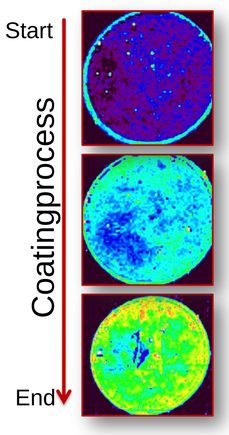
Non-invasive product quality analysis of solid dosage forms was carried out with spectral selective Raman Mapping (left) on a RamanStation 400 (PerkinElmer) and near-infrared spectroscopy (right) FT-NIR Spectrum 400 (PerkinElmer) to investigate coating homogeneity and the distribution of active pharmaceutical ingredient (API) and excipients.

Principle of Raman chemical imaging for the spatial analysis of pharmaceutical products, here demonstrated for tablets analysis. Inhomogeneous API (ASA) and excipient (LM) distributions within tablets are identified via Raman spectroscopy by selecting spectral regions with characteristics of the investigated substance.





Analysis of coating homogeneity:



Spatial resolution of Raman images:

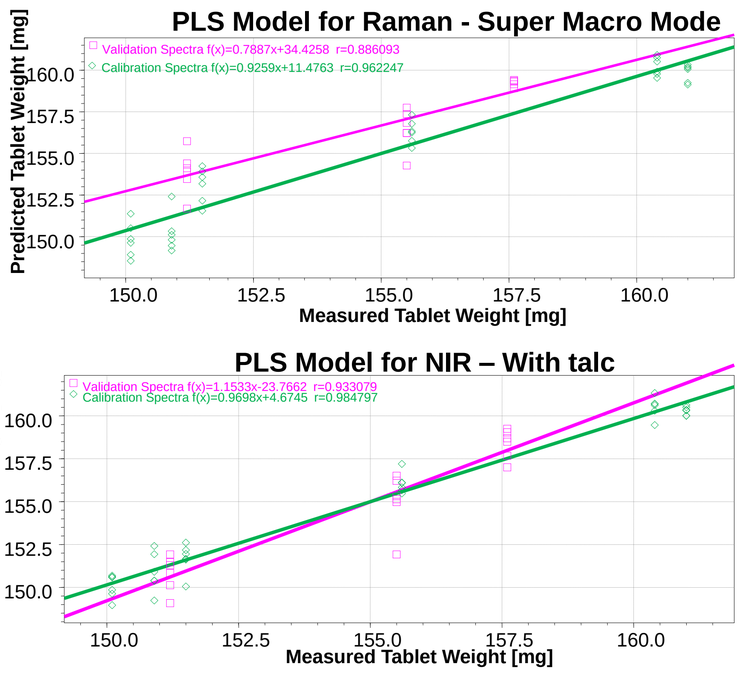
- **100µm excitation spot size – spot power ~100mW (785 nm)**
- **Stage movement >1µm - typical 50 µm**
- **Scan Modes: *Mapping, Line, Super Macro* and *Single Point***
- **Raman auto-focus for bulged surfaces - typical +/-1 mm**

Raman spectra were collected in a range of 200 – 3,278 cm^{-1} at a spectral resolution of 2 cm^{-1} and an integration time of 1 s, with an accumulation of 3 spectra at each position.

Results

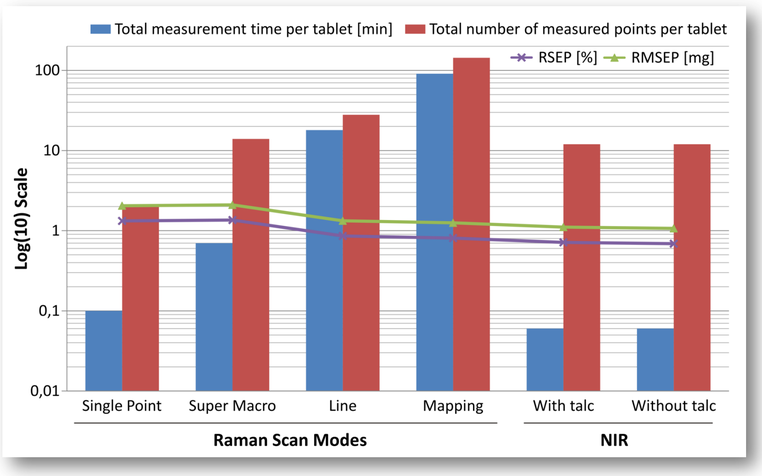
A quantitative (Partial Least Squares Regression - PLS) multivariate data analysis (MVDA) model for the tablet coating thickness was developed on basis of tablets sampled from different stages of a coating process. Calibration was carried out by monitoring weight gain, which is also used in industrial quality control. An evaluation of four different sampling modes *Mapping*, *Line*, *Super Macro* and *Single Point* was performed. In accordance, NIR measurements with a fiber optical reflectance probe showed a RMSEP of 1.07 mg, representing a good correlation between the two methods.

Data Analysis and Model Building



Comparision of the Performance of different Measurement Methods

The root mean square error of prediction (RMSEP) of the different sampling methods showed 1.25, 1.33, 2.1 and 2.05 mg for *Mapping*, *Line*, *Super Macro* and *Single Point* measurement respectively. Although the RMSEP of the *mapping* mode is the smallest, it does not compensate for the much longer measurement time. Raman chemical mapping is conditionally applicable for the determination of coating thickness, but it is not a rapid standard method.



		RAMAN				NIR	
		SP	SM	Line	Mapping	With talc	Without talc
Root mean square error of prediction	RMSEP [mg]	2,05	2,10	1,33	1,25	1,11	1,07
Relative standard error of prediction	RSEP [%]	1,32	1,36	0,86	0,81	0,72	0,69

Conclusions

- **Near-infrared and Raman spectroscopy were shown to be suitable for quantitative analysis and characterization of tablet coatings**
- **Different Raman scan modes *Mapping*, *Line*, *Super Macro* and *Single Point* were evaluated in terms of Partial Least Squares Regression (PLS) model performance.**
- **Raman spectroscopy requires longer integration times to reduce the noise level compared to NIR spectroscopy, but the results show similar model errors.**
- **By using a measurement probe with an extended detection area, Raman spectroscopy could also be applied for fast in-line monitoring of tablet coatings.**

References

[1] Heigl N, Koller D M, Hörl G, Khinast J G, Assessing the Component Distribution Homogeneity of Tablets by Raman Chemical Mapping and Determining the Coating Thickness by FT-NIR and varying Raman Spectroscopic Sampling Approaches by means of Multivatiate Calibration; in preparation

[2] Kauffman J F, Dellibovi M, Cunningham C R. Raman spectroscopy of coated pharmaceutical tablets and physical models for multivariate calibration to tablet coating thickness. J Pharm Biomed Anal 43 (2007) 39-483

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