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Robust monitoring of pharmaceutical manufacturing operations based on combined NIR and Raman spectroscopy

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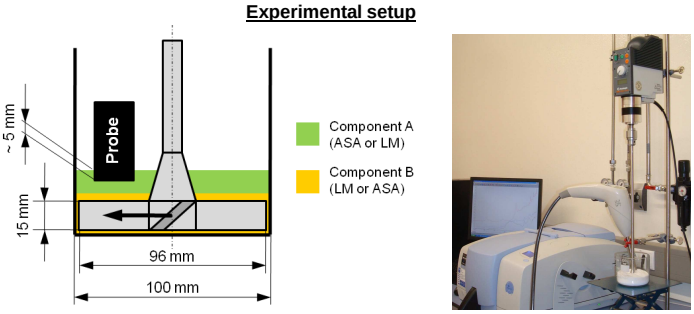
Introduction

Blending processes are one of the key manufacturing steps in pharmaceutical preparation, as optimal blend homogeneity is crucial to ensure correct dosage. Driven by the Process Analytical Technology (PAT) initiative, spectroscopic techniques like near-infrared (NIR) and Raman spectroscopy are implemented for online monitoring and process control [1,2]. Thereby the traditional offline approach, controlling the mixing end-point using HPLC or UV-VIS spectroscopic methods can be bypassed. Here, NIR and Raman spectroscopy were used to evaluate the homogeneity of a binary powder blend consisting of acetyl salicylic acid (ASA) and lactose monohydrate (LM) during the blending process.

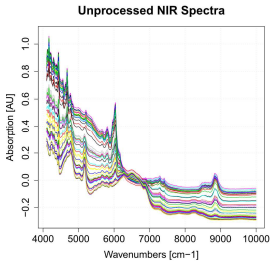
Methods

Experimental setup



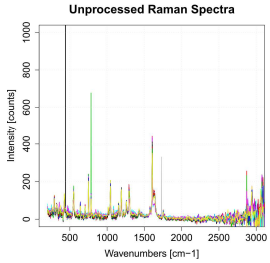
Schematic illustration (left) and photo (right) of the experimental setup, showing a circular mixer with a four plate impeller. The mixer was subsequently filled with either component A or B on top. The fiber optical reflection probe was positioned with direct contact to the powder during the blending process. For our measurements we used the Perkin Elmer spectrometers Spectrum 400 FT-NIR and RamanStation 400F.

NIR spectra measured online



NIR Spectra were collected in a range of 4,100 - 10,000 cm^{-1} at a spectral resolution of 16 cm^{-1} and an integration time of 0.35 s.

Raman spectra measured online

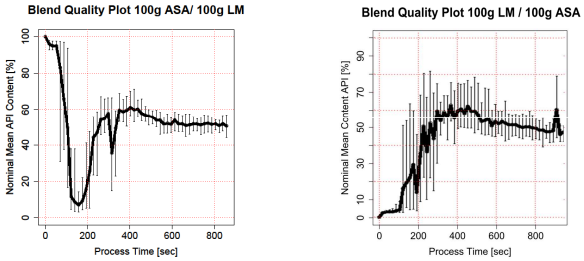


Raman spectra were collected in a range of 200 - 3,000 cm^{-1} at a spectral resolution of 2 cm^{-1} and an integration time of 2 s.

The diagrams show the unprocessed NIR and Raman spectra collected during the blending process. The according mixing parameters were as follows: 100 g ASA / 100 g LM, mixing speed 4 rpm, mixing time 900 s

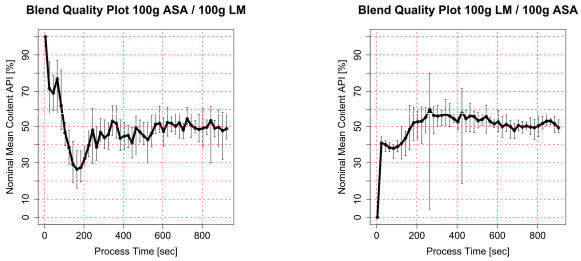
Results

Online Monitoring by NIR



NIR blend quality plots for the two cases of mixer loadings: ASA/LM (left) and LM/ASA (right). Error bars represent the extreme values within an averaging interval of 17.5 s.

Online Monitoring by Raman



Raman blend quality plots for the two cases of mixer loadings: ASA/LM (left) and LM/ASA (right). Error bars represent the extreme values within an averaging interval of 40 s.

Application of powerful preprocessing functions and model building algorithms for analysis of multivariate collinear NIR and Raman data enables online monitoring and process control [3]. Both monitoring systems show similar mixing trends with respect to the prior powder loading sequence: ASA/LM and LM/ASA.

Conclusions

- **NIR and Raman spectroscopy proved to be suitable for quantitative online monitoring of powder blending processes.**
- **Monitoring pharmaceutical operations involving solid samples, NIR and Raman applications are limited by mixture sub sampling. A multiple sample-point approach would increase the robustness of the prediction.**
- **Raman spectroscopy requires longer integration times to reduce the noise level compared to NIR spectroscopy, hence monitoring by Raman spectroscopy is limited to slow alternating processes.**
- **Depending on the powder loading order and volume, different blender specific mixing kinetics were identified.**

References

[1] Berntsson O., Danielsson L.-G., Lagerholm B. and Folestad S., 2002, Powder Technology 123, 185 -193

[2] Sekulic S., Ward H., Brannegan D., Stanley E., Evans C., Sciavolino S., Hailey P. and Aldridge P., 1996, Anal. Chem. 68, 509-513

[3] Blanco M., Romero M. and Alcala M., 2004, Talanta 64, 597-602

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