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NIR Spectral Analysis in Twin-Screw Melt Granulation: Effects of Binder Content, Screw Design, and Temperature

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INTRODUCTION & AIM

Twin-Screw Melt Granulation (TSMG) is a continuous technique that provides more consistent product quality than batch processes [1,2]. In this context, Process Analytical Technology (PAT), including **Near-Infrared (NIR) spectroscopy**, allows real-time monitoring of granule properties and critical quality attributes [1,3]. In this work, NIR spectra were acquired in-line from granules as they fell onto a continuously moving conveyor belt downstream of the TSMG, simulating a continuous monitoring scenario.

🎯 **The objective of this study** was to assess the use of NIR combined with chemometrics to predict PEG content, distinguish granulated from non-granulated samples produced with different screw configurations, and evaluate the effect of on the spectra of outlet temperature. Spectra were preprocessed using **SNV (Standard Normal Variate)** and **derivatives. PCA (Principal Component Analysis)** was applied to explore variability related to screw design and process temperature, and **PLS (Partial Least Squares)** regression was evaluated for PEG content.

METHOD

Materials

Initial particles: α-Lactose monohydrate HMS (NZ) (Chutrau S.A.C.I.F, DFE PHARMA, New Zealand), d_{50} = 0.038 mm

Binder: PEG 6000 (Sistemas Analíticos S.A, Argentina), [0.105-0.25] mm

TSMG →

Granules

Equipment

Twin-screw granulator (Three-Tec ECO ZE 9)

Luminar 5030 Hand-held Miniature AOTF-NIR Analyzer

Conical probe
0.5–1 cm above conveyor belt

Absorbance mode
(1100–2300 nm)

Operating variables (OVs): binder content, temperature, screw configuration and screw speed.

Investigated variables (IVs): binder content, outlet temperature and screw configuration.

Effect of screw configuration →

OVs: 15 w.%, 73°C, **KC**, 175 rpm

OVs: 15 w.%, 73°C, **CC**, 175 rpm

Kneading Element (KE) | Conveying Element (CE) | Comb-mixing Element (CME)

CC configuration: only CEs

KC configuration: 2 KE

Both configurations started with 110 mm of CEs, followed by 12 interchangeable elements (13.5 mm), and ended with a CME followed by a CE. In KC, the KE was positioned at the 6th slot within the interchangeable section.

Effect of PEG content (wt.%) →

OVs: **10 w.%**, 73°C, KC, 100 rpm

OVs: **20 w.%**, 73°C, KC, 100 rpm

Effect of outlet temperature (°C) →

OVs: 15 w.%, 73°C, KC, 175 rpm, **outlet temperature**: **~25°C**

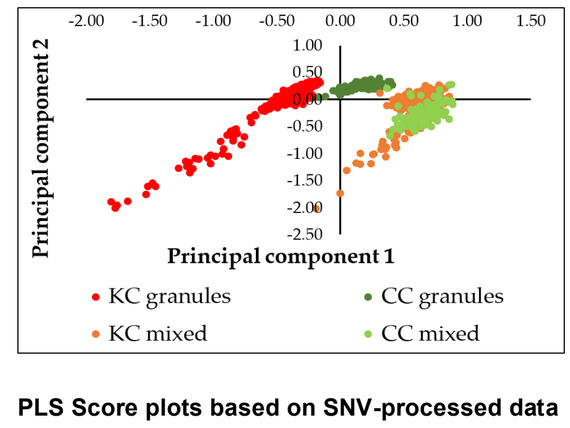
OVs: 15 w.%, 73°C, CC, 175 rpm, **outlet temperature ~30°C**

RESULTS & DISCUSSION

Effect of Screw configuration

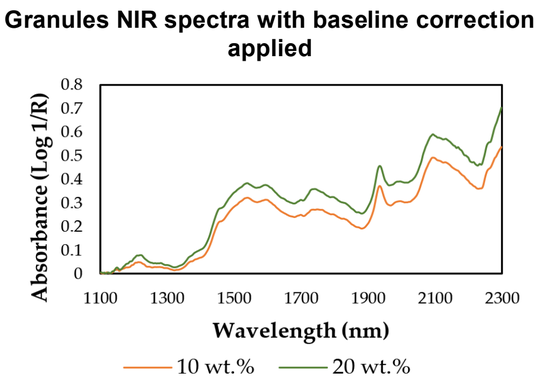
✅ **PCA** of the 1400–1900 nm region (raw & SNV) clearly discriminated granulated (KC granules or CC granules) from non-granulated samples (KC mixed or CC mixed) and screw configurations in granulated runs (KC granules or CC granules).

PCA score plots based on SNV-processed data



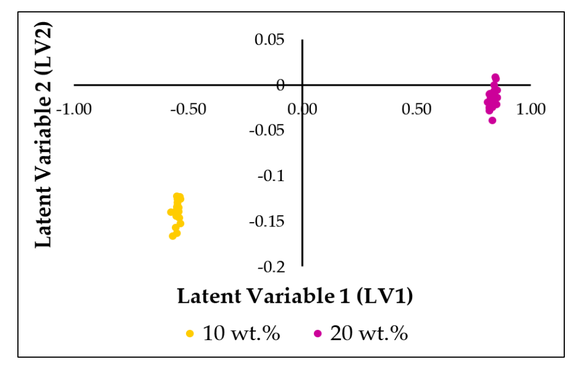
Effect of PEG content (wt.%)

Granules NIR spectra with baseline correction applied



✅ **Raw** and **baseline-corrected NIR spectra** of granules with 10 wt.% and 20 wt.% of PEG show PEG-dependent differences, especially above 1400 nm; higher PEG content increases baseline offset due to larger particle size.

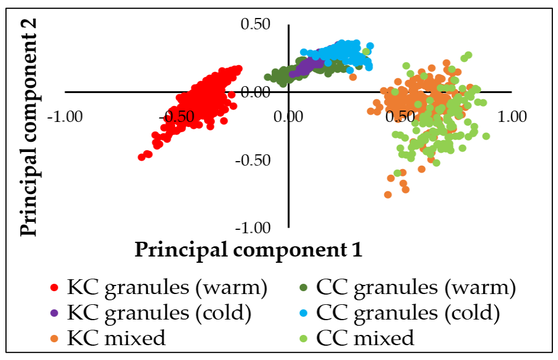
PLS Score plots based on SNV-processed data



✅ **PLS models** showed high fit for PEG content prediction (raw R^2 = 0.9998; SNV R^2 = 0.9983); PLS-SNV was chosen for robustness despite slightly lower R^2, demonstrating reliable in-line NIR prediction.

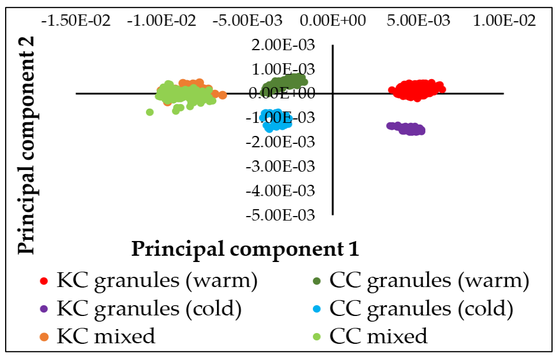
Effect of outlet temperature (°C)

PCA Score plots based on SNV-processed data



✅ **PCA** of raw and SNV spectra distinguished granulated (KC granules or CC granules) from non-granulated samples (KC mixed or CC mixed). SNV improved clustering.

PCA Score plots based on First Derivative-processed data



✅ **PCA** of first- and second-derivative spectra improved separation of warm and cold granules in both screw configurations.

None of the applied techniques were able to distinguish between mixing modes for non-granulated samples.

CONCLUSION

🏆 NIR spectroscopy coupled with PCA and PLS effectively monitored TSMG process, predicting PEG 6000 content (R^2: raw = 0.9998, SNV = 0.9983), distinguishing granulated vs. non-granulated samples, and capturing differences related to screw configuration and granule outlet temperature, highlighting its potential as a robust, non-invasive PAT tool.

FUTURE WORK / REFERENCES

1. Bandari, S.; Al Shaal, L.; Velaga, S.; Repka, M.A. Continuous twin screw granulation—An advanced alternative granulation technology for use in the pharmaceutical industry. *Int. J. Pharm.* **2020**, *580*, 119215.
2. Kittikunakorn, N.; Liu, T.; Zhang, F. Twin-screw melt granulation: Current progress and challenges. *Int. J. Pharm*. **2020**, *588*, 119670.
3. Zhao, J.; Tian, G.; Qu, H. Pharmaceutical application of process understanding and optimization techniques: A review on the continuous twin-screw wet granulation. *Biomedicines*. **2023**, *11*, 1923.