NIR-Based Real-Time Content Monitoring in SSE 3D Printing

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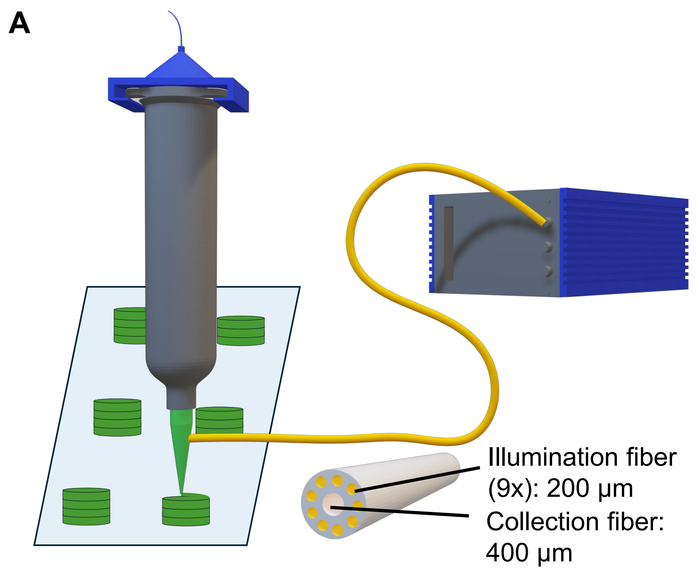
INTRODUCTION

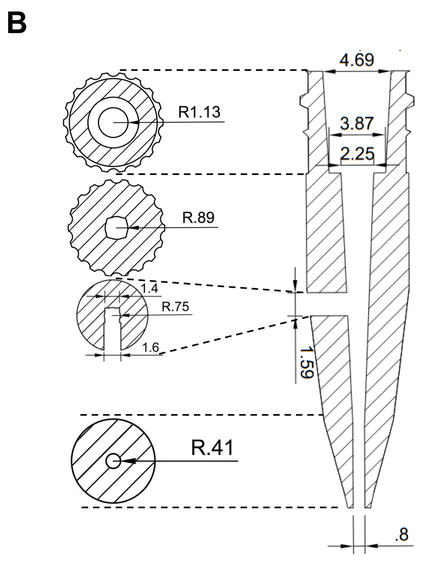
Semi-solid extrusion (SSE) 3D printing offers a promising approach for manufacturing personalized medicinal products by enabling precise dose adjustment while avoiding limitations associated with thermolabile active substances and complex pre-processing steps. In contrast to fused deposition modeling, which requires the preparation of drug-loaded filaments, SSE allows direct printing of drug-containing formulations and is therefore well suited for individualized therapies. [1] In this context, real-time detection of process deviations is essential to ensure consistent product quality and patient safety. To address this need, a near-infrared (NIR) probe was integrated directly into the printing nozzle tip, enabling continuous in-line monitoring of the formulation during printing and providing spectral data for process monitoring and quality control.

MATERIALS AND METHODS

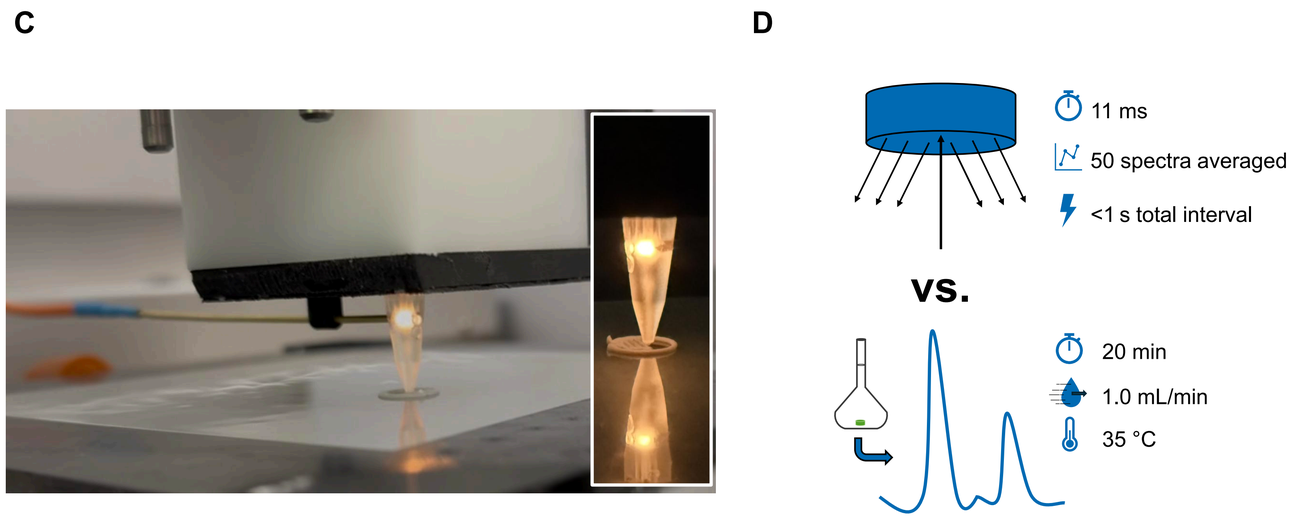
Materials: Croscarmellose (CC) (Kiccolate® ND-2HS) was provided by Asai Kasei (Japan). Hydroxyethylcellulose 10,000 (HEC) (Natrosol® 250 HX) was provided by Ashland (USA). Hard fat (Witepsol® W25) was provided by IOI Oleo GmbH (Germany). Glycerol 85 % and Soy lecithin were purchased from Caelo (Germany).

Methods: Semisolid furosemide-loaded hydrogel and emulgel formulations were successfully prepared and processed into seven-layer printlets using the custom dispensing tip setup.





*A: Schematic representation of the setup implemented in a 3D-Bioplotter (EnvisionTEC). It illustrates the printhead connected to an NIR spectrometer via custom fiber optics, featuring a central collection fiber surrounded by nine illumination fibers for maximum signal capture. **B:** The customized nozzle was printed on a Form 3 SLA printer (FormLabs, Clear Resin V4) at a layer thickness of 0.025 mm.*



*C: Photograph of the printing process with active NIR detection (the nozzle tip is illuminated during in-line spectral data acquisition). **D:** NIR spectral data (11 ms with an averaging of 50 spectra, total measurement interval of <1 s) was cross-validated against traditional destructive HPLC content determination (mobile phase: 56% PBS / 44% methanol, column temperature: 35 °C, flow rate: 1.0 mL/min, method run time 20 minutes).*

RESULTS AND DISCUSSION

Initial NIR spectra already reveal characteristic absorption bands for furosemide, providing the chemical basis for qualitative identification (Fig. 1). Real-time process recording (Fig. 2) confirms continuous data acquisition and the absence of stagnant zones or air gaps at the probe interface. To enhance analytical precision, SNV and first-derivative preprocessing were applied to eliminate physical scattering artifacts and isolate the underlying concentration-dependent signals (Fig. 3). This refined data structure enables both robust qualitative clustering via PCA (Fig. 5) and high-sensitivity quantification through PLS regression (Fig. 4).

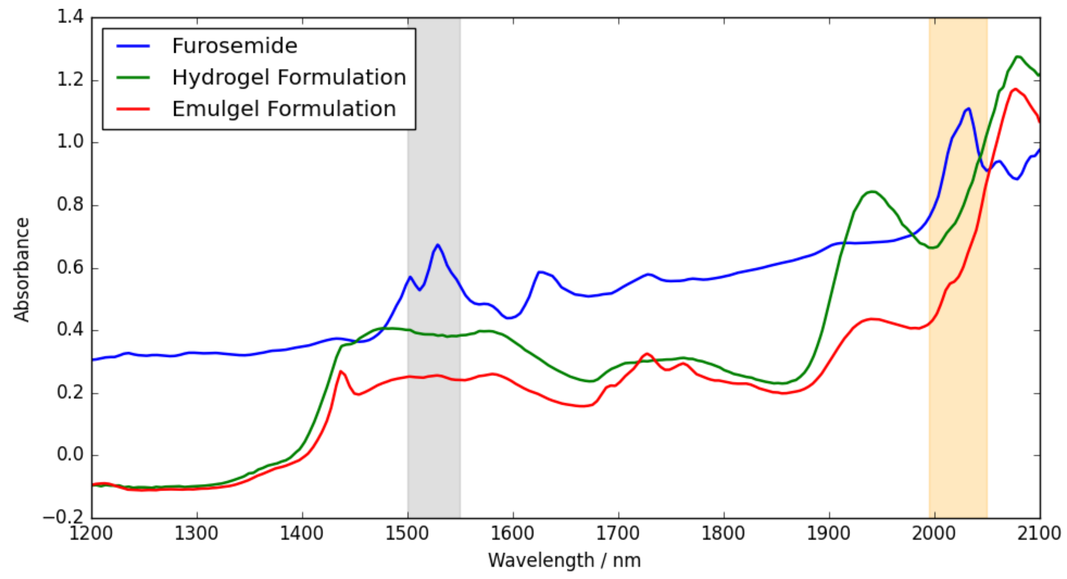


***Figure 1:** NIR absorption spectra (1200–2100 nm). The analysis focuses on the grey (1500–1550 nm) and orange (1995–2050 nm) investigated regions; Characteristic API peaks and formulation-dependent molecular interactions are highlighted.*

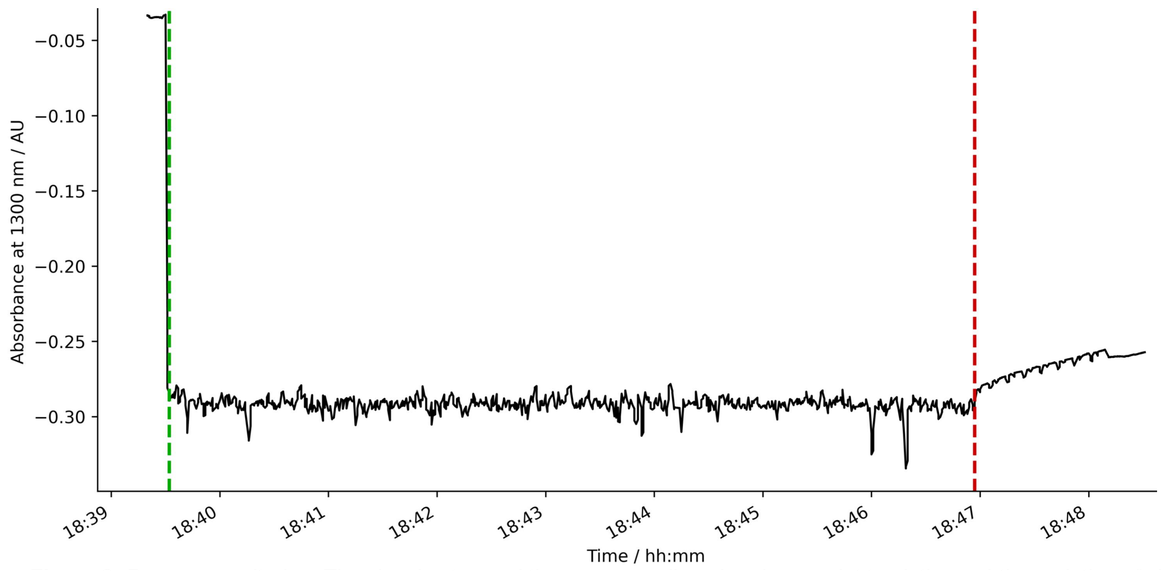


***Figure 2:** Process monitoring: The visual setup and the corresponding absorbance plot track the real-time printing of six emulgel printlets. Green and red line indicate process start and completion, respectively.*

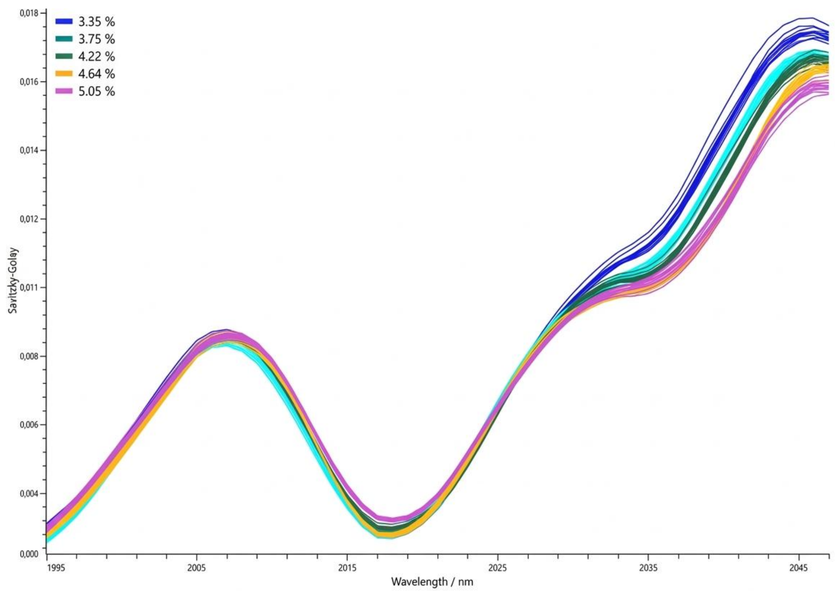


***Figure 3:** Spectral arrangement: Plot showcases the first derivatives of the recorded spectra, which exhibit a clear, sequential arrangement according to furosemide content. These spectra were used for the highly predictive models (hydrogel and emulgel).*

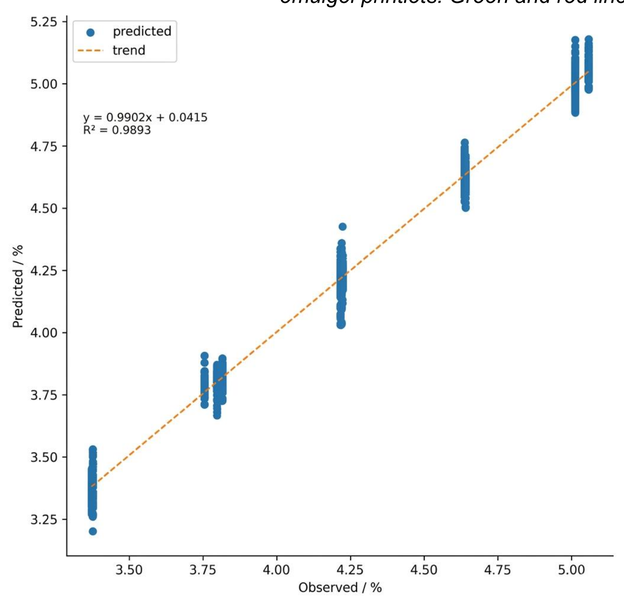


***Figure 4:** Quantification (PLS): Using SNV and first derivative preprocessing (13 smoothing points), the PLS model covers 80% to 120% of the target content (3.35% to 5.05% (m/m)) (emulgel model), demonstrating that even minor fluctuations in concentration are detectable.*

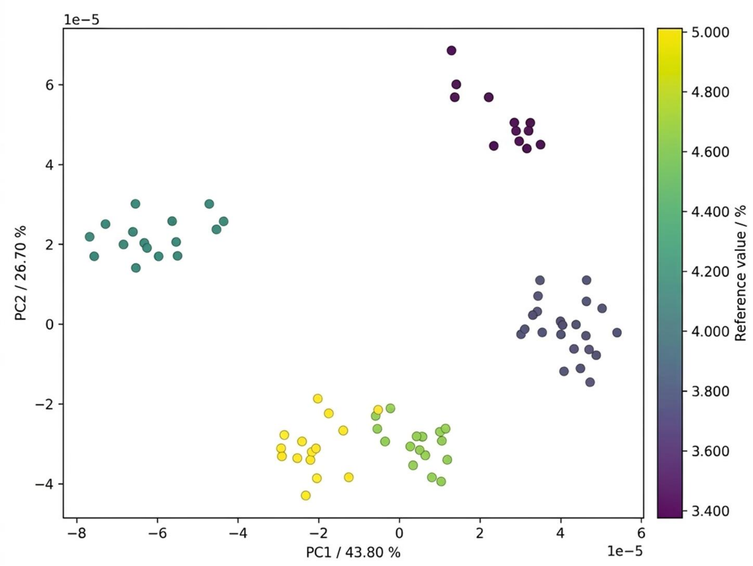


***Figure 5:** Principal component analysis (PCA). Following SNV transformation and first derivative preprocessing (13-point smoothing), the scores plot demonstrates robust and distinguishable clustering. The clear spatial segregation of samples confirms the model's sensitivity in differentiating formulations based on furosemide gradients.*

CONCLUSION

The integrated NIR monitoring setup for SSE 3D printing enables reliable in-line drug content control, offering significant potential to enhance quality assurance in the manufacture of personalized medicines and thereby support improved patient safety and regulatory acceptance. The custom-designed nozzle provides stable process conditions and reproducible NIR spectra. Using furosemide as a model drug, robust PLS regression models ($R^2 > 0.96$) were developed and validated against HPLC reference data, demonstrating the feasibility of continuous drug content monitoring to ensure content uniformity in the resulting dosage forms.

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[1] Rege R, Mellema T, Ramcharan A, Ait A, Verhoeven S, Vibhas V, Jansen, AJ: Ouwerkerk, N. and Shokri, F. 3D drug printing by semi-solid extrusion through reusable cartridges. AAPS PharmSciTech, 26, 1–12 (2025).

[2] Shokraneh F, Filppula AM, …, Sandler Topelius N: Automated 3D printing of pediatric furosemide tablets: A personalized medicine approach using semi-solid extrusion and NIR monitoring. Eur. J. Pharm. Sci., 214, 107269 (2025).