pharmaceutics

Supplementary Materials: Exploring the Complexity of Processing-Induced Dehydration During Hot Melt Extrusion Using In-Line Raman Spectroscopy

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X-Ray Powder Diffractograms (XRPD) of Starting Materials

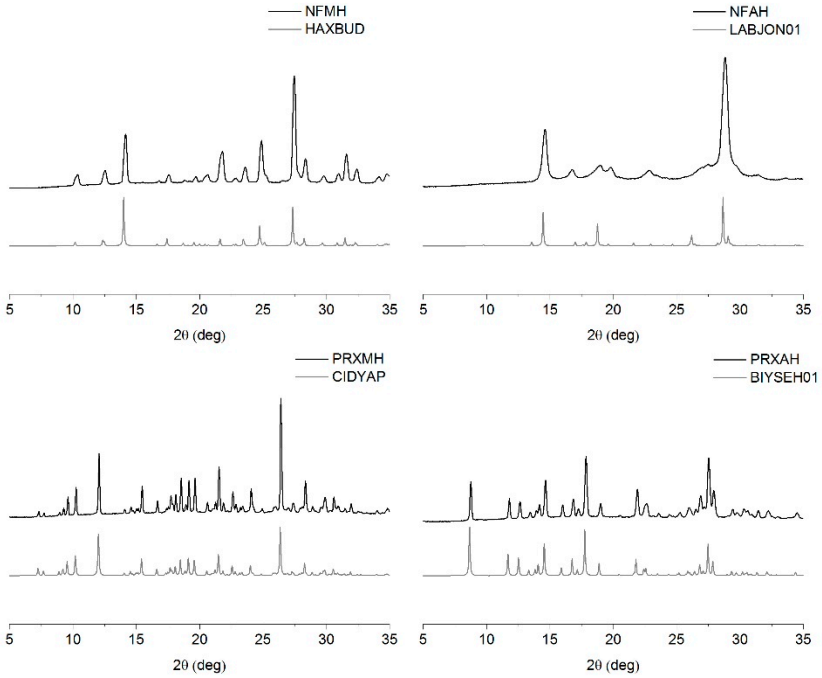

Figure S1. X-ray powder diffractograms (XRPD) of NFMH/PRXMH and NFAH/PRXAH (monohydrate and anhydrate forms of starting materials). HAXBUD/LABJON01/CIDYAP/BIYSEH01 referring to the CSD refcodes.

Raman Spectra of PEO during Extrusion (Matrix Polymer)

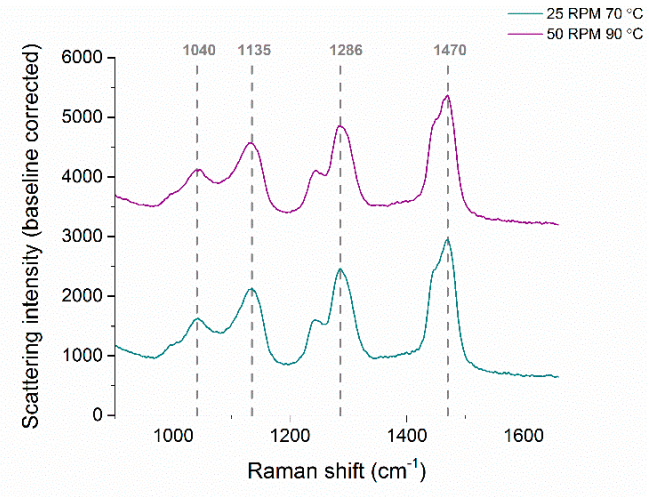

Figure S2. Raman spectra of PEO melts after 10 min of recirculation in the extruder.

Raman Spectra of Nitrofurantoin and Piroxicam (API Raw Materials)

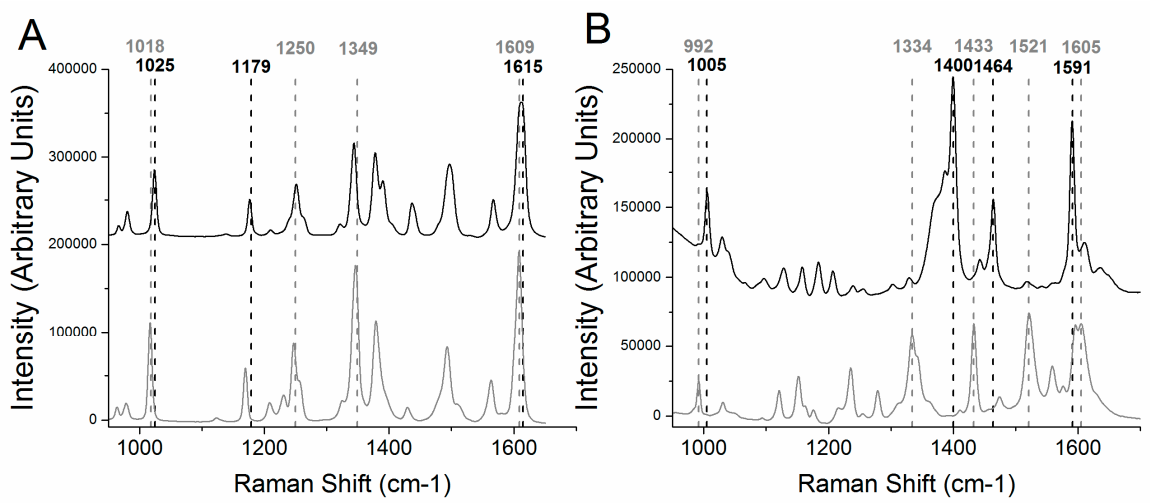

Figure S3. Raman spectra of (**A**) NFMH (black) and NFAH (grey) and (**B**) PRXMH (black) and PRXAH (grey). Dashed lines indicate significant shifts of (**A**) NFMH (black), NFAH form β (grey) and (**B**) PRXMH (black) and PRXAH form I (grey).

Predictive Residual Sum of Squares from PCA Models

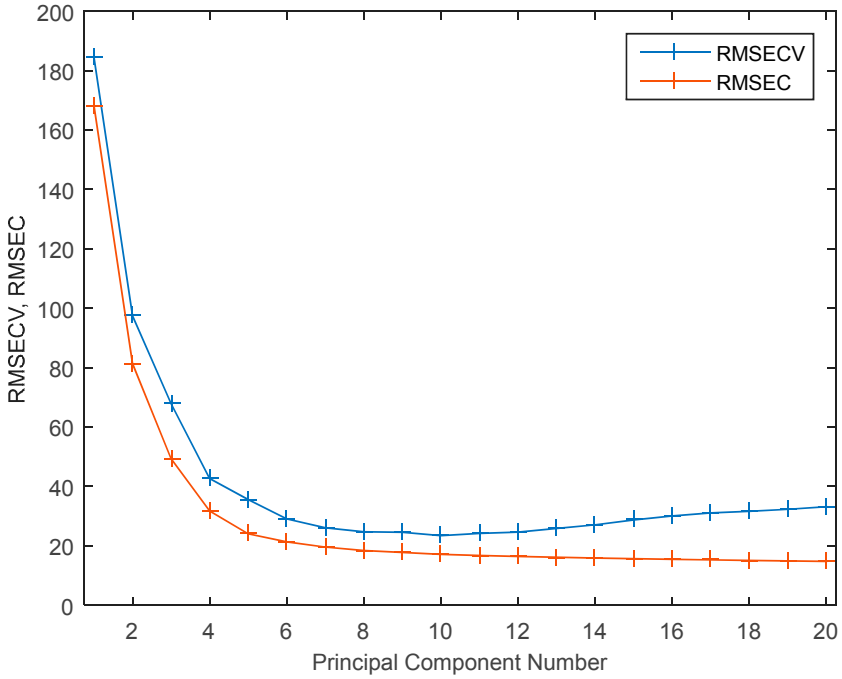

Figure S4. Plot of the residual mean squared error term of the model calibration data (RMSEC, red) and residual mean squared error term of the cross-validation data (RMSECV, blue) for a PCA model on the augmented matrix containing the pre-processed nitrofurantoin dataset.

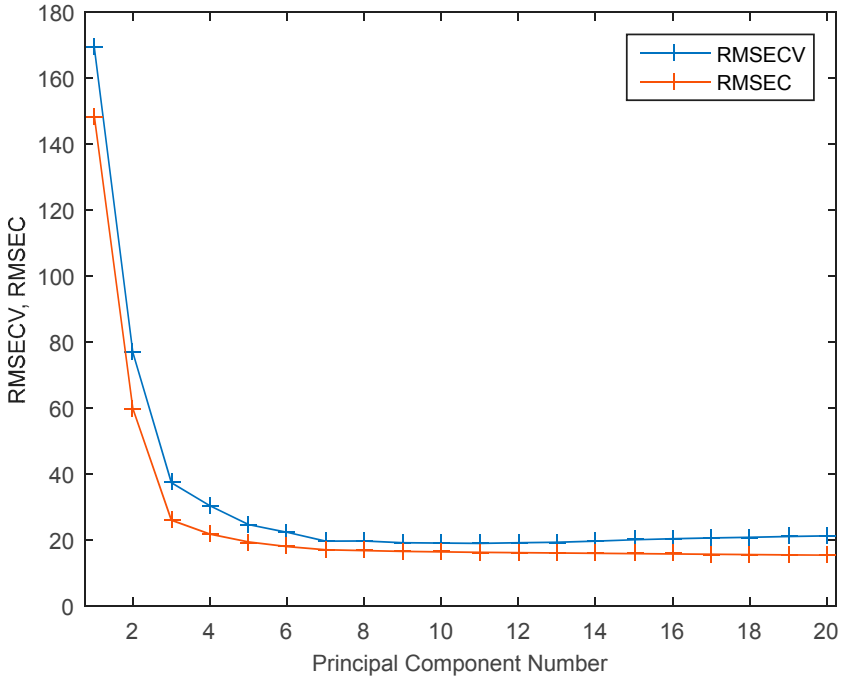

Figure S5. Plot of the residual mean squared error term of the model calibration data (RMSEC, red) and residual mean squared error term of the cross-validation data (RMSECV, blue) for a PCA model on the augmented matrix containing the pre-processed piroxicam dataset.

Frequency Sweeps and Differential Scanning Calorimetry Results

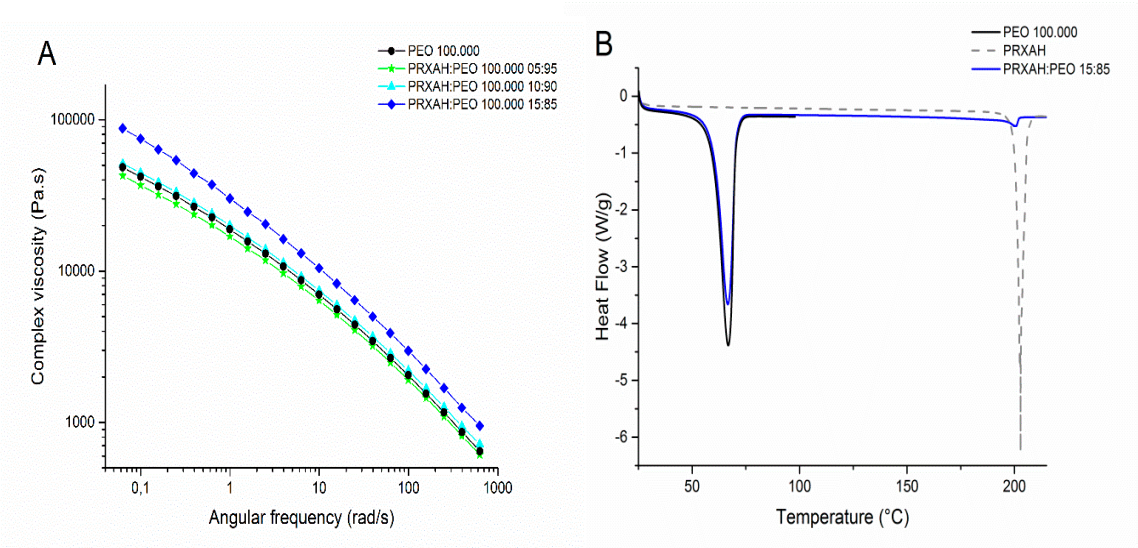

Figure S6. (**A**) Frequency sweep of PEO (black circles) and PRXAH:PEO mixtures at concentrations 05:95 (green stars), 10:90**.** (light blue triangles) and 15:85 (blue squares) at 70 °C. (**B**) DSC thermogram of PEO (black), PRXAH (grey, dashed) and PRXAH-PEO (blue).

Time Sweeps and Force Measurement Results

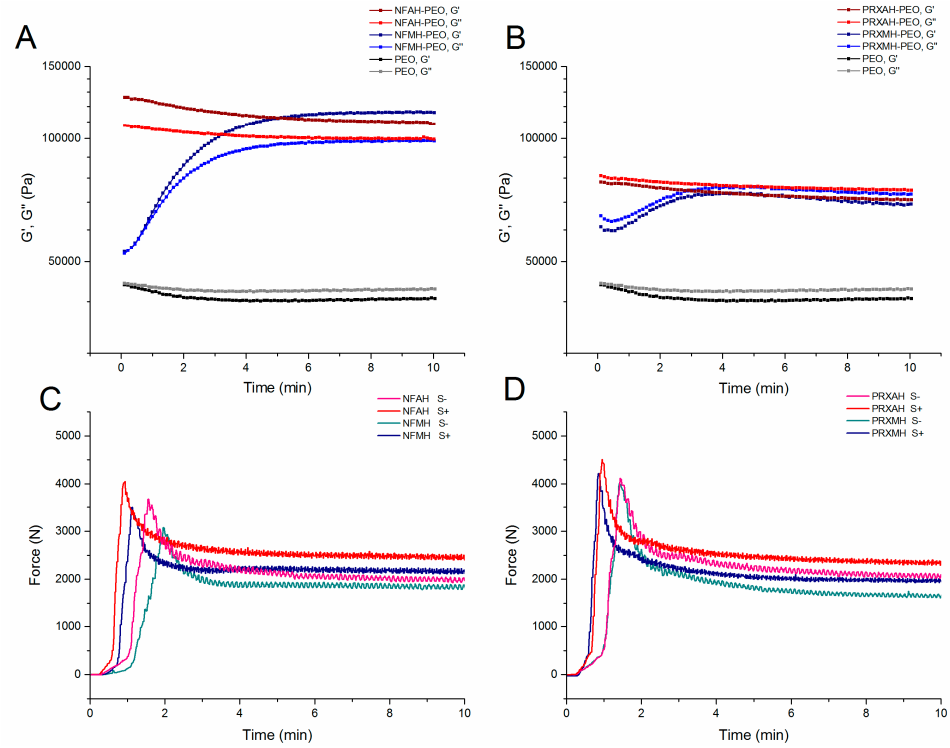

Figure S7. Storage modulus G′ and loss modulus G′′ as a function of time of (**A**) NF formulations and (**B**) PRX formulations, PEO (grey and black), XXMH-PEO (navy and blue) and XXAH-PEO (wine and red); Force during extrusion of (**C**) NF formulations and (**D**) PRX formulations, XXAH-PEO (red and pink) and XXMH-PEO (blue and cyan). All measurements are conducted at 70 °C, S−: 25 rpm and S+: 50 rpm.

Table S1. Force exerted on screws in Newtons at timepoint 600s during extrusion, reported as average values with standard deviation in parentheses, $n = 3$.

	NF 25 rpm		NF 50 rpm		PRX 25 rpm		PRX 50 rpm	
	70 °C	90 °C	70 °C	90 °C	70 °C	90 °C	70 °C	90 °C
AH	2048 (52)	1493 (-) [a]	2424 (22)	1950 (29)	1999 (73)	1467 (37)	2343 (9)	1728 (56)
MH	1807 (68) *	1420 (74)	2183 (62) *	1771 (72)	1666 (49)*	1184 (23) *	1964 (15) *	1330 (29) *

[a] One missing value. * $P < 0.05$ in a two-sample t-test against the corresponding AH experiment.

Experimental, SAOS Rheometry

Small Amplitude Oscillatory Shear (SAOS) tests were performed on an AR-G2 strain-controlled rheometer fitted with an Environmental Testing Chamber (both TA Instruments, New Castle, DE, USA) using a stainless steel 25 mm plate-plate geometry, with a trim gap of 1.0 mm and a geometry gap of 0.8 mm. Rotational mapping of the instrument and zero-gapping was performed prior to each test. Each sample was loaded onto the pre-heated lower plate in powder form. The upper plate was then lowered to 0.2 mm above the experimental gap width (0.8 mm), excess molten material was trimmed along the edge of the plates, and the upper plate was lowered to 0.8 mm. Oscillation amplitude sweeps were performed to determine the linear viscoelastic region (LVE) of the materials at a set temperature of 70 °C, 60 s of oscillatory pre-shear at 10 rad/s, an angular frequency of 10 rad/s, sweeping from 0.015% to 15% strain. Oscillation frequency sweeps were performed at a set temperature of 70 °C, 0.5% strain (within LVE), over an angular frequency range of 0.01 to 100 Hz (0.06–628 rad/s) with 5 points per decade. All frequency sweep tests were measured in triplicate. Oscillation time sweeps were performed at a set temperature of 70 °C, 0.5% strain, at an angular frequency of 10 rad/s for duration of 600 s. All time sweep tests were measured in triplicate.