Comparison of XRD, NIRS and DSC to Quantify Small Amounts of Amorphous Lactose in a Crystalline Matrix and Vice Versa

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Introduction

During production or processing of pharmaceutical solids, such as milling, spray drying or lyophilisation, disruption or activation of the crystalline structure can lead to the formation of amorphous regions. These regions show a couple of different properties which can influence their processing behaviour or affect the performance of the finished product: an enhanced dissolution rate and chemical instability, the ability to form solid solutions or the sensitivity to solid state transformation to the crystalline form [1, 2]. Therefore it is necessary to investigate the existence and amount of amorphous material within a crystalline matrix and vice versa. Different methods are compared with respect to the precision, accuracy, detection limit and speed of measurement: X-Ray Diffraction (XRD), Near Infrared Spectroscopy (NIRS) and Differential Scanning Calorimetry (DSC).

Materials

Alpha-lactose-monohydrate was used as a model substance. Samples to be taken 100% crystalline were stored at a relative humidity of 56% and 30°C for one week to ensure a complete recrystallisation of any amorphous regions present [1]. Samples of amorphous lactose were prepared by lyophilisation of a saturated lactose solution.

Spectra (XRD, NIRS and DSC) were obtained of the pure crystalline and amorphous form and of binary mixtures: with an interval of 10% (10-90%) and an interval of 1% (1-9% and 90-100%).

XRD

X-Ray Diffraction scans (figure 1) were obtained using a X´Pert PRO MPD system (PANalytical B.V., Almelo, the Netherlands) with Cu *Kα* radiation (40 kV, 40 mA), Bragg Brentano focusing optics and the X´Celerator as detector.
Measuring conditions were as follows:

- Mixture 0-100%: 0.008 step size, 3 min/ meas., 4-40° 2θ
- Mixture 1-9%: 0.016 step size, 2 min/ meas., 7-45° 2θ
- Mixture 90-100%: 0.008 step size, 6 min/ meas., 12-13° 2θ

The evaluation of the data was done with PANalytical´s X´Pert HighScore software for phase identification.

NIRS

Reflectance spectra (figure 2) were taken with a Bruker Optik Vector 22/N FT NIR spectrometer with fiber optics. The NIR instrument recorded the mean spectrum of 32 scans of each sample over a wave number region of 3800 – 12000 cm^{-1}, which took 30 s/measurement. The regression model for the samples was calculated by PLS after data preprocessing by vector normalisation and first derivative.

DSC

Measurements of the crystallisation energy (figure 3) were carried out on a Perkin Elmer Pyris 1 Differential Scanning Calorimeter using sealed aluminium pans at a scanning rate of 10°C/ min. Each measurement took about 15 min.

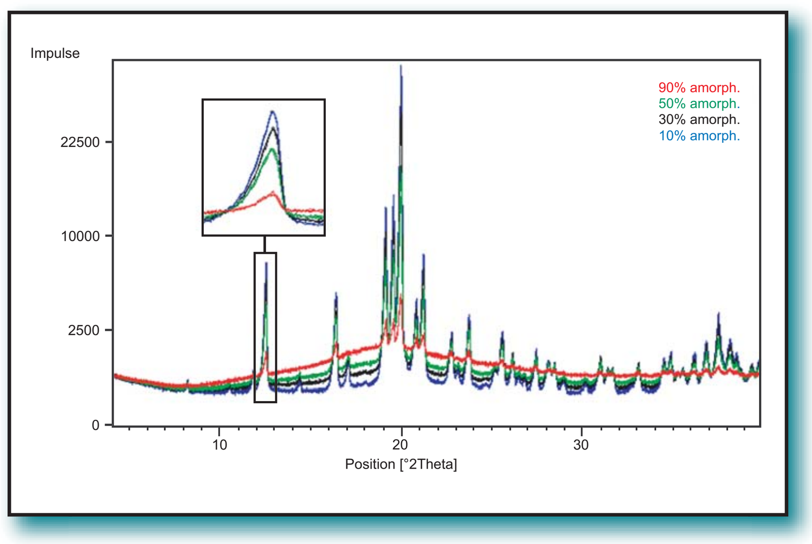

Fig. 1: XRD scans of different binary mixtures of amorphous and crystalline lactose

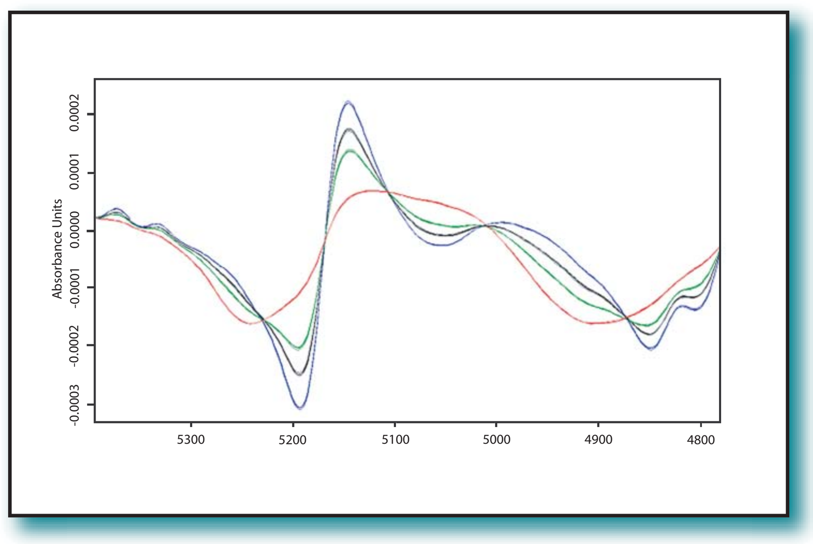

Fig. 2: NIRS spectra of different binary mixtures of amorphous and crystalline lactose

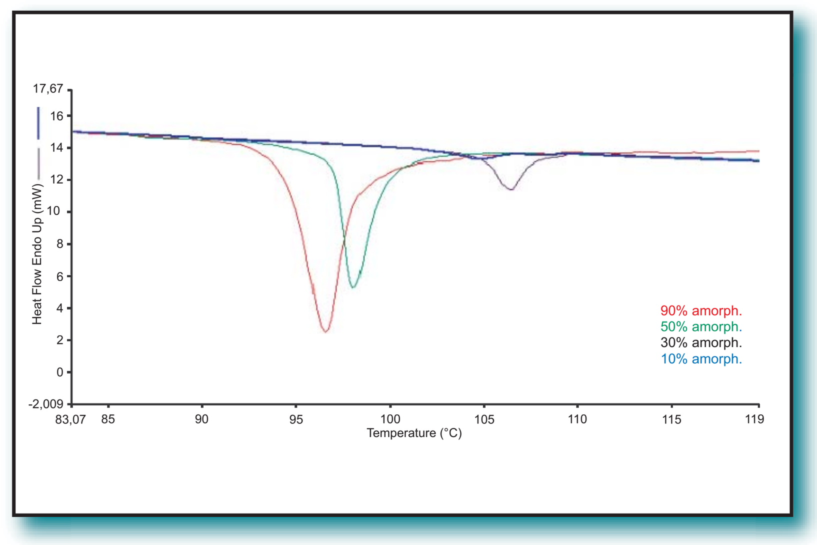

Fig. 3: DSC scans of different binary mixtures of amorphous and crystalline lactose

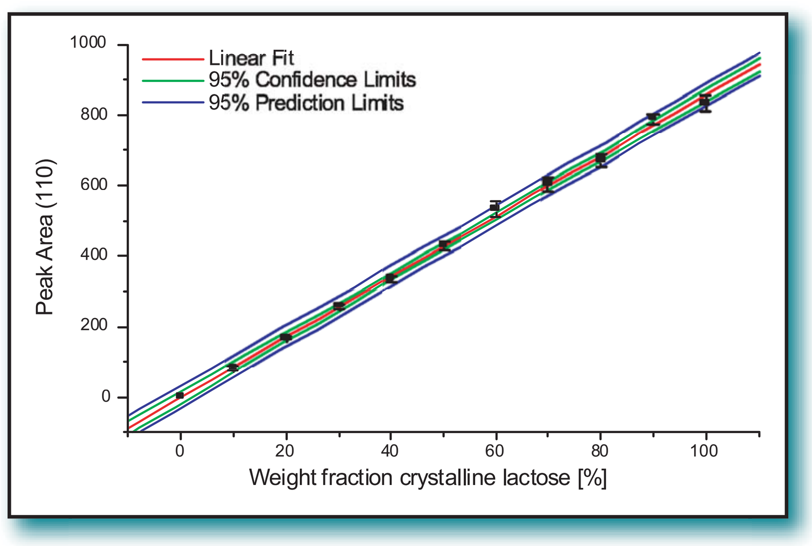

Fig. 4: XRD calibration curve, 10% intervals

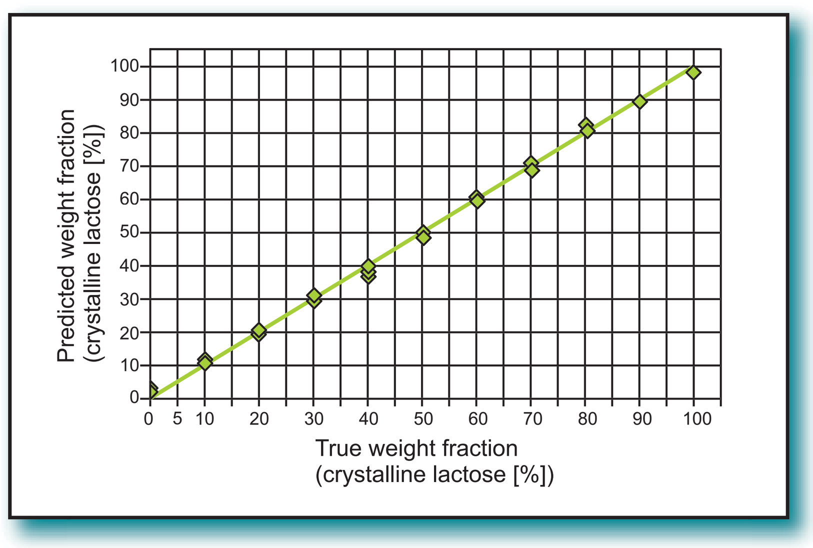

Fig. 5: PLS regression of the NIRS data, 10%

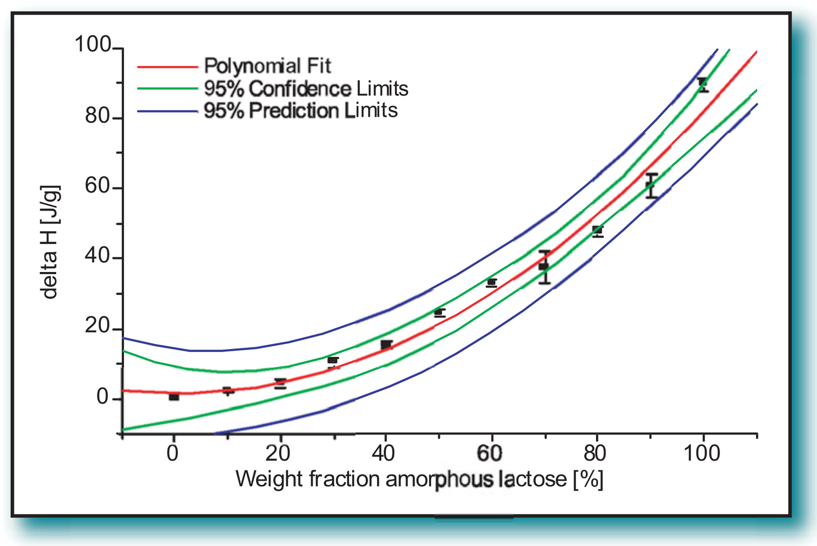

Fig. 6: DSC calibration curve, 10% intervals

Discussion

	0-100% cryst. content			1-10% cryst. content		1-9% amophous content	
	XRD	NIRS	DSC	XRD	NIRS	XRD	NIRS
R^2	0.9981	0.9975	0.9611	0.9981	0.9945	0.9872	0.9939
Precision[% rel. StDev.].	1.75-6.43	0.15-19.6	1.02-21.2	3.74-27.72	3.13-61.63	1.14-35.5	0.07-0.64
Bias [%]	2.36 to 2.43	2.95 to -1.9	3.51--4.45	0.225 to -0.29	0.28 to -0.23	0.52 to -0.47	0.57 to -0.3
RMSECV [%]		1.54			0.26		0.253
Rank		4			2		2
Detection limit [%]				0.5	0.5	1	<1
Time/meas. [Min]	3	0.5	15	6	0.5	2	0.5

Fig. 4 to 6 show the calibration curves for the binary mixtures of amorphous and crystalline lactose in intervals of 10% for the three methods. The XRD and NIRS calibrations have an excellent linearity with a correlation coefficient of better than 0.99 and a detectability down to about 0.5%. Precision and accuracy decrease for samples containing less than 10% crystalline material, where XRD is more precise than NIRS. The DSC results show no linearity and therefore need polynomial fit, precision and bias are reduced for amorphous contents higher than 70%, for contents lower than 20% the sensitivity decreases.
For small amounts of amorphous lactose XRD and NIRS reveal good linearity and accuracy with a detectability down to 1%, where NIRS is more precise.

Conclusion

XRD and NIRS are excellent techniques to determine small amounts of amorphous material in a crystalline matrix and vice versa. Though NIRS is faster than the other methods, it usually requires a time consuming calibration e.g. with XRD.
Measurements of the crystallisation energy (DSC) are too inaccurate to be used for quantification, probably due to the incomplete crystallisation of the amorphous part.

References:
[1] A. Saleki-Gerhardt, C. Ahlneck, G. Zografi, Int. J. Pharm. 101 (1994) 237 – 247
[2] E. Suihko, V.-P. Letho, J. Ketolainen, E. Laine, P. Paronen, Int. J. Pharm. 217 (2001) 225 - 236

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