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Introduction

Within the last decades a new subgroup of diluents, so called Co-processed Excipients (CPE), found its way into pharmaceutical practice [1]. After a seemingly endless discussion about their definition, state, and boundaries to a simple physical admixture (PAM), CPE have been defined as a combination of two or more compendial or non-compendial excipients designed to physically modify their properties in a manner not achievable by simple mixing. Thereby, a significant chemical change has to be excluded [2]. Typically, CPE offer a benefit beyond the simple admixture, may be manufactured by a specialized process, where spray-drying is the most frequently used platform. However, little is known about the intensity of such physical modifications defining a CPE, and causing its functional supremacy over its corresponding PAM. The crucial question is, down to which particle level physical alterations in raw materials have to take place for achieving additional blend performance? What are the smallest structural particle units necessary for e.g., synergies in compaction, disintegration, or lubrication behavior? The aim of this study was to compare the samples inner morphology and crystallinity before and after co-processing by means of Small and Wide-Angle X-ray Scattering (SWAXS) technique using relative scale invariant calculation of parameters such as surface volume (Sv) or correlation length (Cl).

Materials & Methods I

As a representative example a well-established, spray-dried CPE, comprising commonly used pharmaceutical raw materials Lactose Monohydrate (75%), and MCC (25%) was chosen. MicroceLac[®] 100, its corresponding PAM, as well as, the raw materials have been applied, as depicted in **Table 1**.

Blend Type	Components	Trade Name	Manufacturer	Lot-Production Date
Co-processed (CPE)	Lactose Monohydrate, 75 %, MCC, 25 %	MicroceLac [®] 100	MEGGLE	L103150922A537 D060S0592
Physical Admixture (PAM)	Lactose Monohydrate, 75 %, MCC, 25 %	none	–	6072023
Raw Material I	Lactose Monohydrate, 100 %	GranuLac [®] 200	MEGGLE	8032022
Raw Material II	MCC, 100 %	Vivapur [®] 101	JRS	66101216647

Table 1: SWAXS tested samples

Materials & Methods II

For preparation of the PAM a Turbula[®] Mixer (Bachofen, Switzerland) was used (t = 15min, 34 rpm). Samples were prepared for SWAXS analytics in a multiple sample holder and measured with Xenocs Xeuss 3 System using micro-focus source: Genix3D (Power: 50 kV @ 0.6 mA, Energy: Cu Ka 8.04 keV, Wavelength: 0.154189 nm/1.54189 Å). The SAXS detector used, was an Eiger 4M (Dectris) and the sample to detector distance was 1800 mm (Collimation: slit 1: 0.3 mm x 0.3 mm and slit 2: 0.15 mm x 0.15 mm). For WAXS measurements identical adjustments in detector, energy, powder, source, and wavelength were used, whereas the sample to detector distance was 55 mm (Collimation: slit 1: 0.6 mm x 0.6 mm and slit 2: 0.3 mm x 0.3 mm). Basically, 4 different samples have been evaluated, the CPE vs. its corresponding PAM, and the single raw materials Lactose Monohydrate, and MCC. All samples were measured in triplicate and then averaged, background noise subtracted and evaluated to satisfying analytical statistics.

Results I

An overlap of SAXS spectra of all samples is represented in **Figure 1** in a log/log scale for Porod parameter evaluation [3, 4].

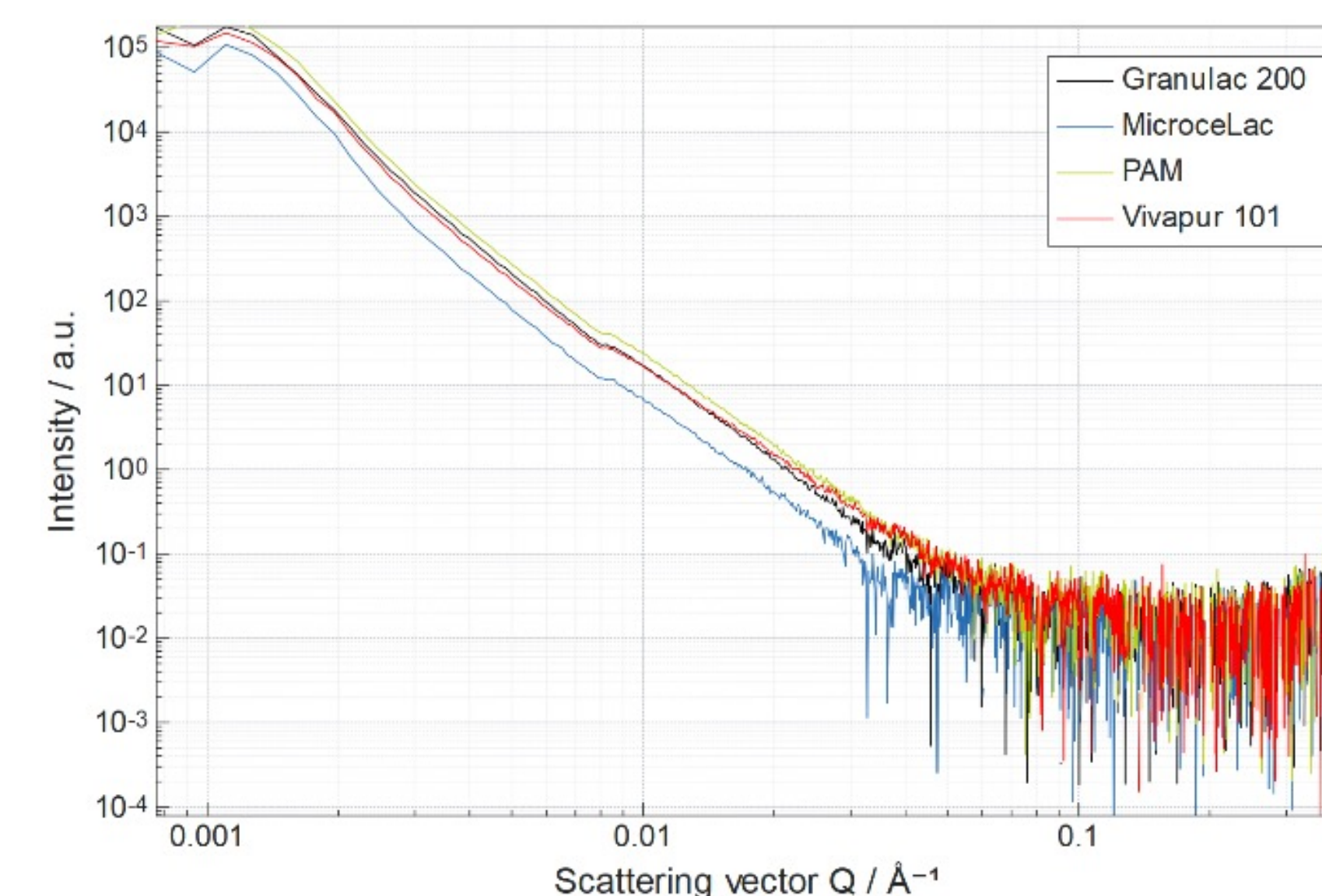


Figure 1: Overlap of SAXS spectra from all materials of Table 1

Results II

A key issue was to compare the internal morphology of the CPE, PAM, and its corresponding raw materials in order to gain insight into the impact of co-processing on lowest level. Therefore, we decided to estimate the parameters of Porod's law on one scale for all samples. The Porod fit was applied to the SAXS parameters, such as surface to volume ratio for the practical relative scale using relative invariant method and Xenocs XSACT software [3, 4]. To make valid comparisons, an identical fit range was chosen: 0.0100 - 0.313 Å⁻¹ on the log/log domain phase, Sv, or correlation length or size (diameter) of the spherical nano domains, Cl, was determined. Sv can be interpreted as a parameter for homogeneity in terms of the electron density differences distribution of a material [3].

Results for 4 investigated samples are listed in Table 2, the values show a clear ranking: Sv value of 1.043 ± 0.007 e-02 nm⁻¹ is lowest for co-processed product MicroceLac[®] 100, indicating the highest degree of uniformity of all investigated samples. This result correlates to a Cl of 575.3 nm of spherical nano domains. With a Sv value of 1.127 ± 0.005 e-02 nm⁻¹ (Cl 532.3 nm) raw material GranuLac[®] 200 comes closest to CPE MicroceLac[®] 100. PAM showed a Sv of 1.674 ± 0.008e-02 nm⁻¹ (Cl of 358.3 nm) and is found on third position. Raw material Vivapur[®] 101 is defined by a maximum in inhomogeneity, expressed by a Sv of 2.453 ± 0.014 e-02 nm⁻¹ (Cl 244.6). A slightly different value to GranuLac[®] 200 is also expected due to its different chemical composition.

Blend Type	Sample	SAXS Sv (nm ⁻¹)	SAXS Cl (nm)
Co-processed (CPE)	MicroceLac [®] 100	1.043 ± 0.007 e-02 nm ⁻¹	575.3
Physical Admixture (PAM)	PAM	1.674 ± 0.008 e-02 nm ⁻¹	358.3
Raw Material I	GranuLac [®] 200	1.127 ± 0.005 e-02 nm ⁻¹	532.3
Raw Material II	Vivapur [®] 101	2.453 ± 0.014 e-02 nm ⁻¹	244.6

Table 2: SAXS Sv, surface to volume ratio for the practical domain phase, and correlation length (Cl) or size (diameter) of the spherical nano domains of CPE MicroceLac[®] 100, the corresponding physical admixture (PAM), and raw materials GranuLac[®] 200 and Vivapur[®] 101

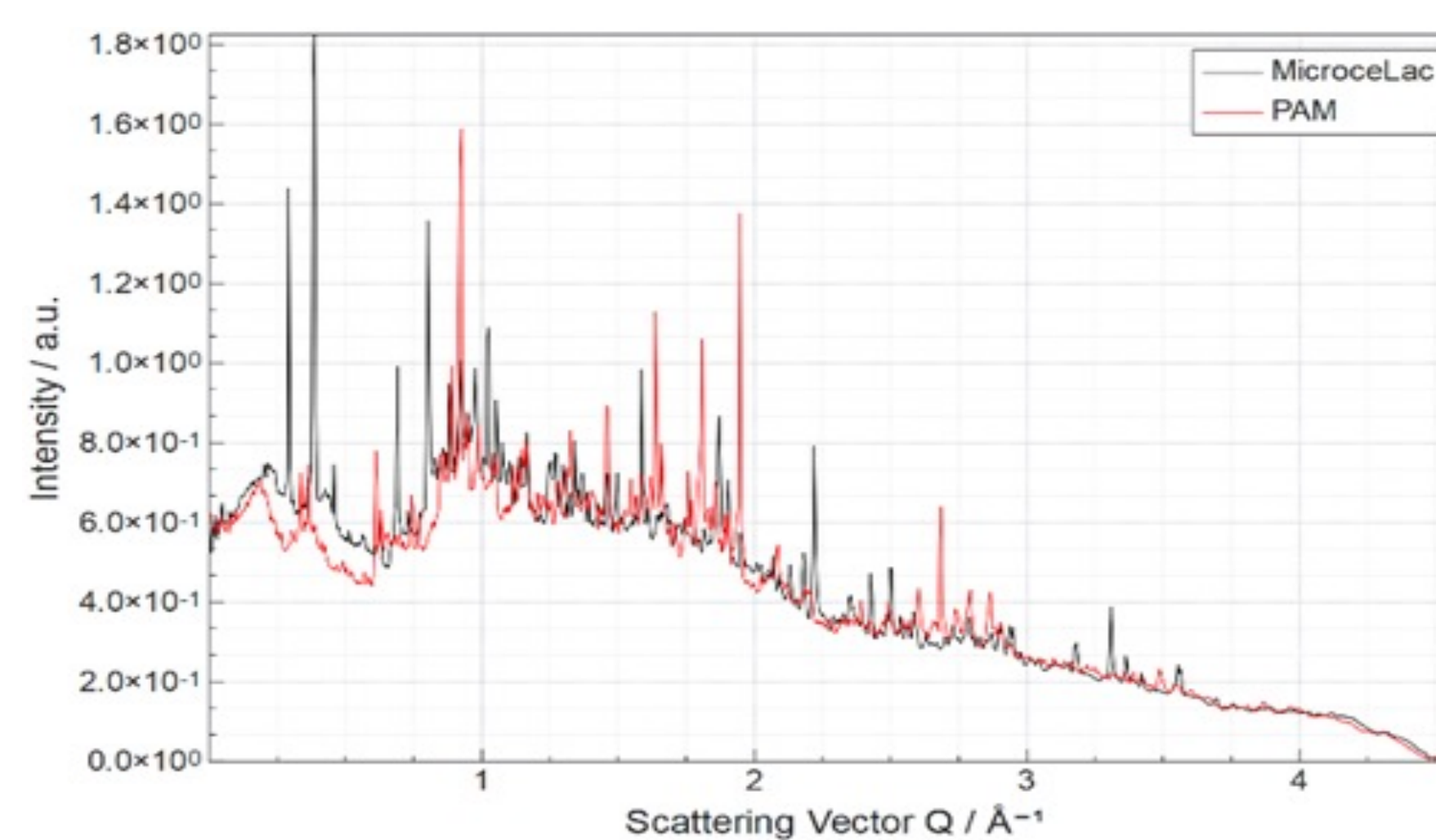


Figure 2: Overlap of WAXS spectra showing MicroceLac[®] 100 (black line) and PAM (red line)

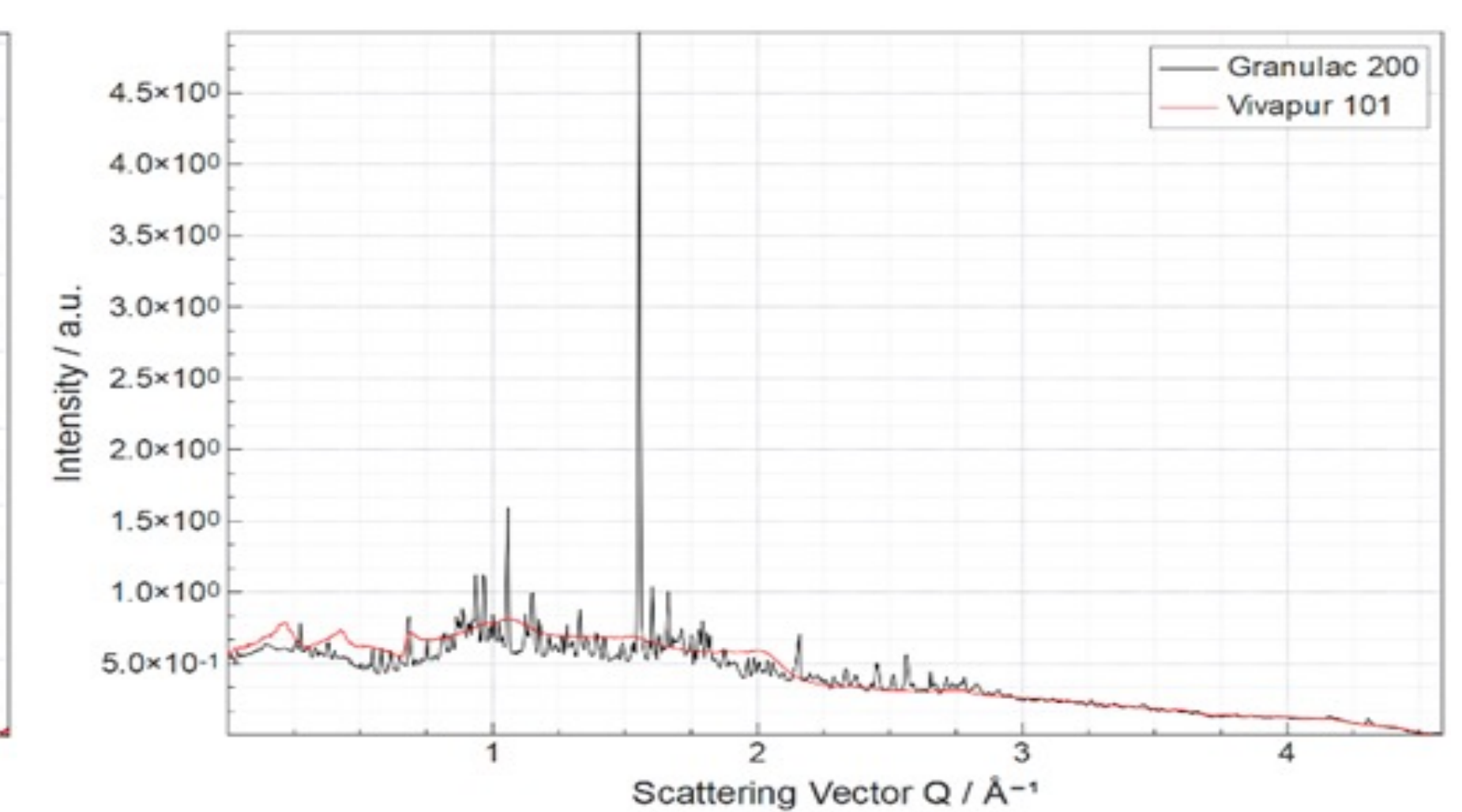


Figure 3: Overlap of WAXS spectra of raw materials Lactose Monohydrate (GranuLac[®] 200, black line) and MCC (Vivapur[®] 101, red line).

In addition to SAXS, WAXS was performed separately. An overlap of CPE and PAM spectra suggests that the applied production process for CPE MicroceLac[®] 100 does not significantly impact crystallinity. Since no rotating capillary device for statistical validation was on hand, an accurate evaluation of all peaks was not possible [5]. However, it may be seen that in both products crystallinity is present to a similar extent (**Figure 2**).

But in the WAXS signals of the raw materials, an obvious difference in crystallinity is visible. MCC grade Vivapur[®] 101 shows a weaker crystalline structure mixed with an amorphous signal (**Figure 3**).

Conclusion

The information derived by SAXS elucidates that during co-processing (spray-drying) of example material MicroceLac[®] 100, structural evolution in terms of an increase in homogeneity down to the nano level takes place. Such a high uniformity in inner morphology is neither reached by the separate raw materials Lactose Monohydrate and MCC, nor by the corresponding PAM, as expressed by surface to volume ratio (Sv), and correlation length (Cl). It is interesting to note that the raw materials initial crystallinity remains intact during co-processing, as indicated by WAXS.

References:

- Penz, F. K., Co-prozessierte Excipientien. Pharm. Ind. 81, Nr. 4, 572-578 (2019)
- Co-processed Excipient Guide For Pharmaceutical Excipients. IPEC, www.ipecamericas.org (2017)
- Hodzic A. et al., Effect of process variables on the Small and Wide-Angle X-ray Scattering (SWAXS) patterns of powders, granules and pharmaceutical tablets. Powder Techn. 221, 447-452 (2012)
- Hodzic A. et al., Revealing hidden molecular nanostructure details in the pellet formulation of ibuprofen by combining Synchrotron and laboratory sources. J. Drug Deliv. Sci. Techn. 68, 103114, 1-8 (2022)
- Hodzic A. et al., Small- and wide-angle X-ray scattering (SWAXS) for quantification of aspirin content in a binary powder mixture. Int. J. Pharm. 428, 91-95 (2012)