Application note

Verification of component distribution in pharmaceuticals

Raman imaging highlights how twin-screw extrusion can improve the quality and consistency of tablets

Authors

Dr. Maximilian Ries,
Thermo Fisher Scientific GmbH,
Application Specialist FTIR | Raman

Dr. Ceren Yuece,
Application Specialist Extrusion,
Thermo Electron (Karlsruhe) GmbH

Dr. Margarethe Richter,
Application Specialist Extrusion,
Thermo Electron (Karlsruhe) GmbH

Thermo Scientific DXR3xi Raman Imaging Microscope.

Raman spectroscopy is a non-destructive investigation technique that can identify and differentiate chemical substances on the microscale. In combination with chemometric methods, it provides an analytical toolset based on confocal microscopy and vibrational spectroscopy that allows for the chemical profiling of heterogeneous materials with a precision of less than 1 micrometer.

Advantages of the DXR3xi Raman Imaging Microscope

Ultrafast Raman Imaging with high sensitivity due to location-controlled stage and EMCCD detector

True confocal Raman microscope for diffraction-limited spectroscopy and high wavenumber accuracy

Optimum laser power fine-control to avoid sample damage

Perfect automatic 6-step alignment

OMNICxi imaging-centric software with 3D visualization

thermo scientific

Continuous manufacturing (CM) of pharmaceutical products is becoming a new technological standard in the pharmaceutical industry. Today, most pharmaceutical products are produced by a method known as batch manufacturing in which different operations, such as weighing, mixing, tableting, and encapsulation are performed in separate rooms and at separate times. This is a long, multi-step process that requires large-scale equipment. Continuous manufacturing is faster than batch processing and easier to scale. It eliminates the need to stop and move intermediates between production steps, and thus potentially improves the quality of the final pharmaceutical product.

In this study, the Thermo Scientific™ DXR3xi Raman Imaging Microscope was used to assess the distribution of the components in liquisolid tablets manufactured with different process parameters utilizing a Thermo Scientific™ Pharma 16 Twin-Screw Extruder as a continuous processor. Either simethicone or a combination of simethicone and loperamide hydrochloride were used as active pharmaceutical ingredients (APIs) in the tablets. Detailed compositions of the tablets are provided in Table 1 and Table 2. The particle size distribution (PSD) of the powders prior to manufacturing was analyzed with a dynamic image analysis system. The physical properties of the tablets such as hardness, friability, and disintegration were assessed. The uniformity of dosage was assessed according to USP/NF Chapter <905>[2].

Ingredient	mg/ Tablet	Concentration (%w/wt)	Function
Simethicone Q7-2243 LVA	125.0	17.0	Active ingredient
TRI-CAFOS® 500 (TCP)	374.8	51.0	Carrier
DI-CAFOS® A150 (CDPA)	220.4	30.0	Diluent/ compression aid
Ac-Di-Sol® SD-711 NF	7.4	1.0	Disintegrant
Ligamed® MF-2-V	7.4	1.0	Lubricant
Total	**735.0**	**100.0**	

Table 1. Composition of tablets S1-S3 produced with a twin-screw granulator (TSG) and HSG with a high-shear granulator.

Ingredient	mg/ Tablet	Concentration (%w/wt)	Function
Simethicone Q7-2243 LVA	125.0	16.96	Active ingredient
Loperamide hydrochloride	2.0	0.27	Active ingredient
TRI-CAFOS® 500 (TCP)	375.1	50.90	Carrier
DI-CAFOS® A150 (DCPA)	220.1	29.87	Diluent/ compression aid
Ac-Di-Sol® SD-711 NF	7.4	1.00	Disintegrant
Ligamed® MF-2-V	7.4	1.00	Lubricant
Total	**735.0**	**100.00**	

Table 2. Composition of simethicone and loperamide hydrochloride liquisolid formulation in tablet S4.

The DXR3xi Raman Imaging Microscope used in the present study was equipped with an electron-multiplied CCD operating at 600 Hz and a 532 nm laser providing 40 W power at the sample. Raman mapping was performed with 25 µm lateral resolution using an Olympus 10x MPLN objective and with 5 µm resolution using an Olympus 50x LMPLFLN objective. Raman spectra were collected at a rate of 400 Hz and with 40 repetitions. Typical collection times were approximately 1 hour for 5 µm mappings of 1x1 mm^2 and 6 hours for 25 µm mappings of 12x12 mm^2.

Multivariate Curve Resolution (MCR) was applied as a chemometric method with background subtraction and five estimated compounds to allow the algorithm to find the individual components in samples S1-S3 and HSG; see Table 1. For simplicity, from here onward TRI-CAFOS® 500 and DI-CAFOS® A150 are abbreviated as TCP and DCPA, respectively. For sample S4, loperamide hydrochloride was added as a sixth component, and the MCR algorithm was changed accordingly; see Table 2.

Figure 1 depicts the Raman spectra of the ingredients used for preparing the tablet samples. Even though peaks appear in similar spectral regions, e.g., for TRI-CAFOS® 500 and DI-CAFOS® A150, or in the CH-stretching region around 3000 cm^{-1} for the organic components, all spectra can easily be distinguished by eye. Figure 2 shows the spectral maps recorded on the liquisolid tablets prepared in this study. MCR reveals the distribution of individual components in the tablets. Each individual color represents a component or mixture, represented by a model Raman spectrum as seen in Figure 3. It is important to highlight the fact that MCR does not directly identify chemical substances, but it detects a set number of model spectra that represent all spectra in the map. Like on a painter's palette, holding the colors used in a painting, each individual color on the palette can also be a mixture of two pure colors from paint tubes. In the maps in Figure 2, dark blue is a mixture of simethicone and TCP; light blue is a mixture of simethicone and TCP with different concentrations; red is DCPA (sometimes with an addition of simethicone); green is Mg-stearate; orange is croscarmellose sodium; and pink (for S4 formulation only) represents loperamide hydrochloride.

In the top tiles (tiles a through e) of Figure 2 are Raman maps of the entire tablets recorded at a spatial resolution of 25 µm. In two cases, the maps of only half of the tablets were registered but they can be considered very representative. In the bottom part (tiles f through j) are detailed spectral images of 1x1 mm^2 tablet fragments recorded with a spatial resolution of 5 µm.

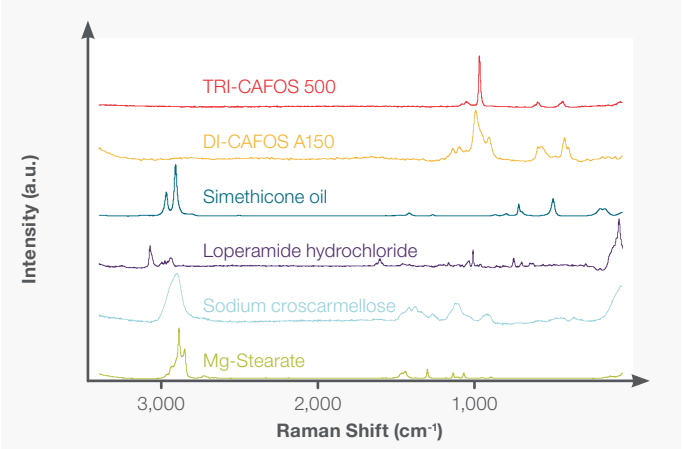

Figure 1. Normalized reference spectra of all ingredients expected in the tablet samples.

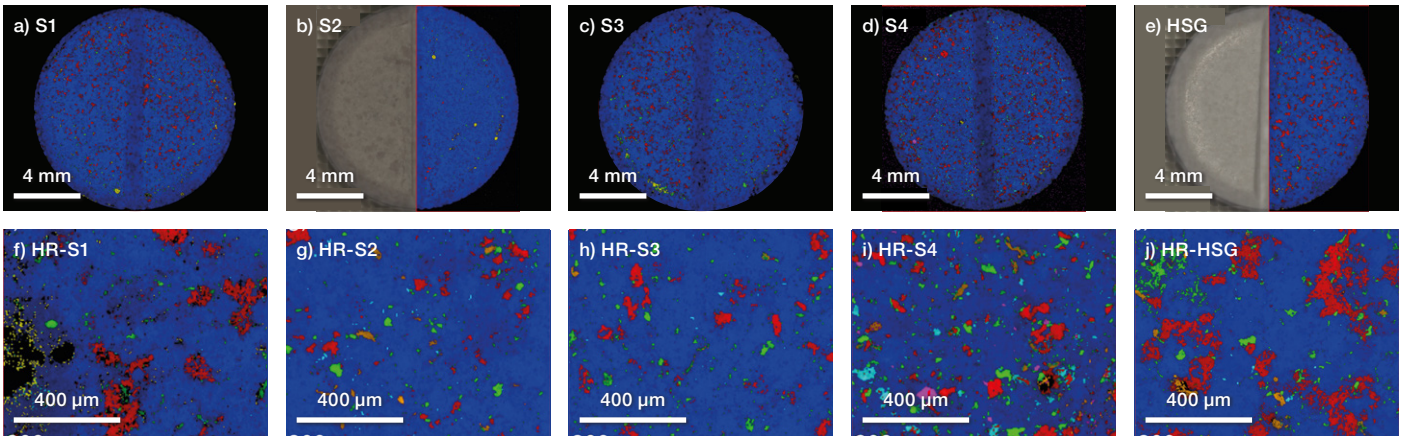

Figure 2. Raman maps of liquisolid tablets registered with 25 µm (top) and 5 µm (bottom) resolutions. The spectra are separated into chemical components by MCR analysis and displayed in assorted colors. Note that the individual components in each map differ slightly. Colors were assigned for each sample to represent the highest conformity across the components of all tablets.

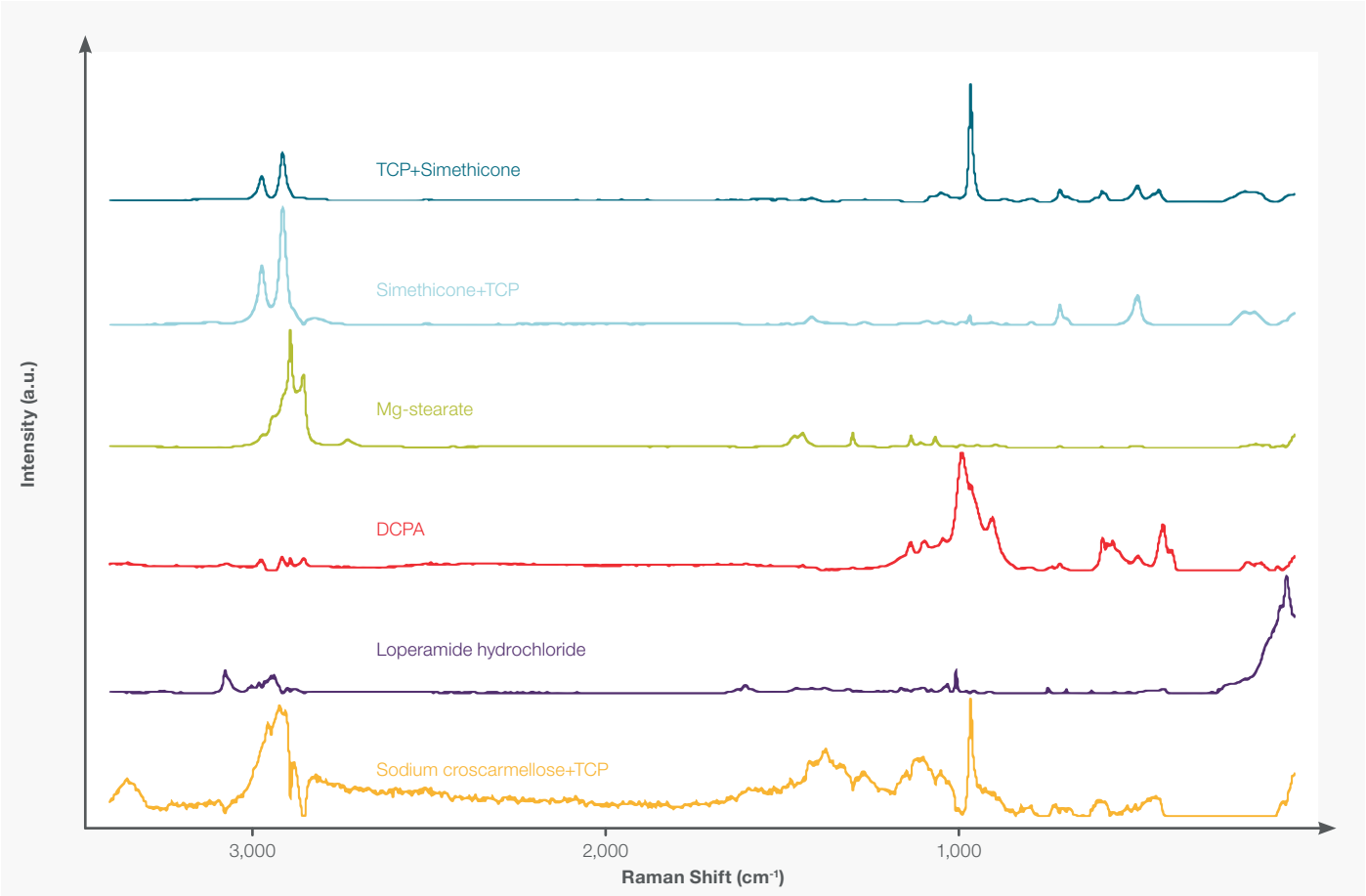

Figure 3. MCR spectra from the 5 µm resolution map of the S4 sample. Colors represent the individual components as displayed in the map in figure 2i). Note that the individual components in each map differ slightly.

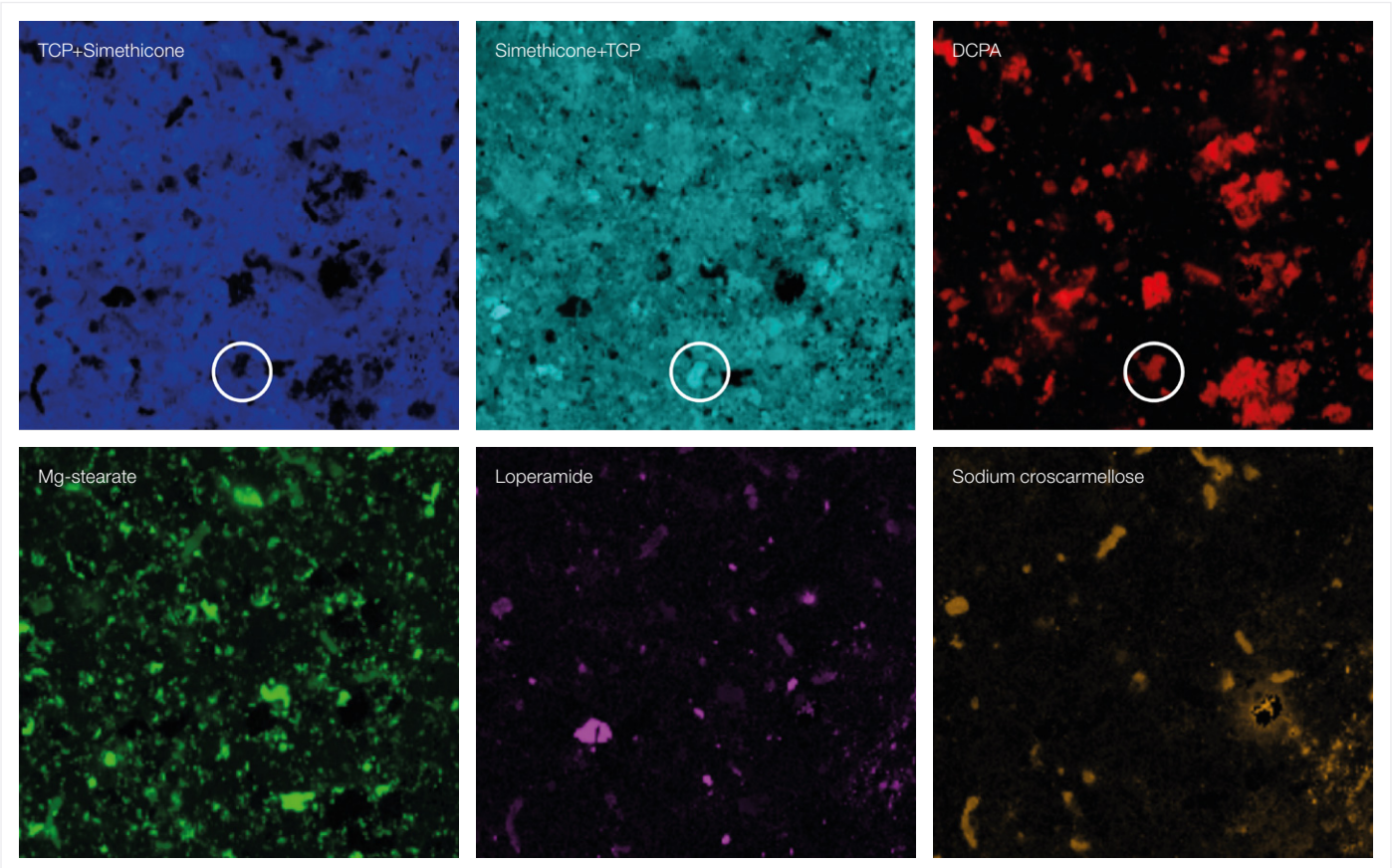

Figure 4. Individual MCR maps of the high-resolution mapping from Figure 2i). The white circle in the upper tiles serves as a guide to the eye.

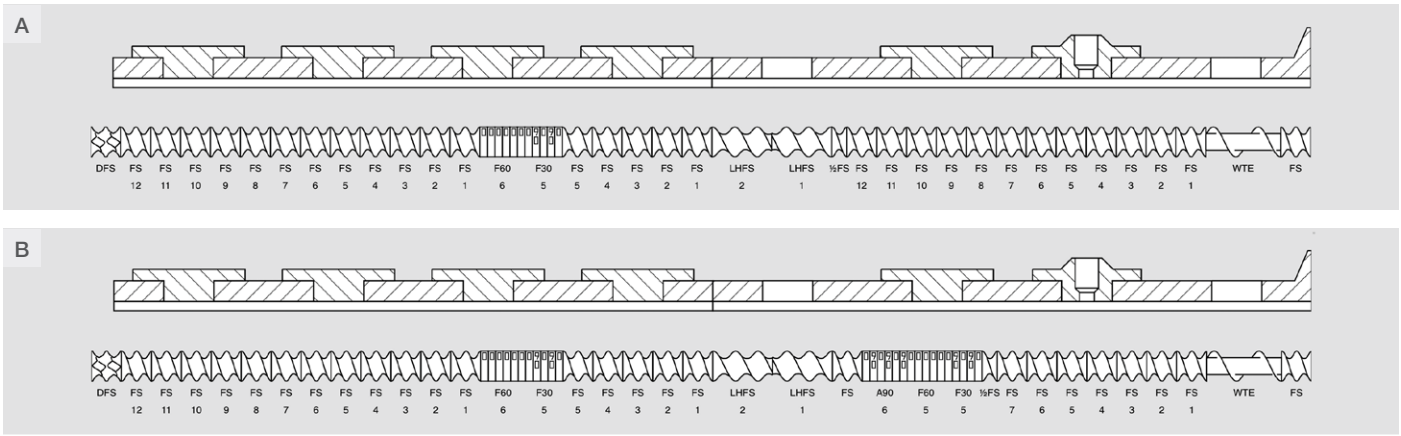

Figure 5. Schematic diagram of the screw configurations used in the TSG.

The areas where the Raman spectra characteristic of DCPA were recorded are marked in red. An analysis of these areas shows how the diverse ways of preparing liquid-loaded powders affect the distribution of components in liquisolid tablets. Distribution strongly depends on the type of granulator used (high-shear granulator (HSG) or twin-screw granulator (TSG)) and, in the case of TSG, on the configuration of the screws (see figure 5), and the speed of the process (i.e., the speed at which the powders were passed through the TSG). Formulations labeled as S1 and S2 were produced at the same low throughput of 5 kg/h: see Table 3. In the case of the first formulation, the screw configuration included only one kneading zone, so the powder mainly resided in the mixing area. This led to the formation of larger agglomerates, which are represented by large red areas on the Raman maps. These observations correlate very well with the results of the particle size analysis, where the largest particles were measured for this formulation. In the case of the second formulation, the screw configuration included two kneading zones. With this setting, the particle size distribution was narrowed, and the distribution of ingredients in the tablet was improved.

In the Raman maps of the S3 formulation, which was produced at a higher throughput of 10 kg/h, the DCPA particles appeared to be slightly larger in size (even though PSD analysis did not reveal increased particle dimensions). Nevertheless, the particles were distributed very evenly throughout the tablet. Raman maps of the formulation prepared by HSG show large agglomerates of DCPA and Mg-stearate particles, which are relatively uniformly distributed in the tablet. Similar conclusions on particle sizes can be drawn from PSD analysis.

In some locations associated with DCPA, the real Raman spectra were not pure but included spectral signatures of simethicone as well. This indicates a local release of simethicone from TCP particles during tableting at higher compression forces. In effect, local breaking and crushing of TCP particles occurred, leading to the release of simethicone. The resorption of simethicone by DCPA particles further prevented it from being squeezed out during tableting. This might seem counterintuitive to the MCR results, as the DCPA component does not contain any signature of simethicone. However, a closer look at the real spectra or at the individual distribution of each MCR component as shown in Figure 4, reveals a high concentration of DCPA and simethicone without much contribution from TCP in the region indicated by the white circle.

A formulation containing loperamide hydrochloride (S4) was produced with the “B” screw configuration at a higher process throughput of 10 kg/h. The spectral map shows a uniform distribution of formulation components, but numerous particles of DCPA+simethicone occurred. This suggests that the higher processing speed may not provide the efficient sorption of simethicone on the carrier particles (TCP). Note that, in the case of this formulation, simethicone additionally contained loperamide hydrochloride, which certainly affected the liquid’s viscosity and the speed of its penetration into the particles of the carrier.

Tablet name	S1	S2	S3	S4
Screw configuration	A	B	B	B
Screw speed (rpm)	200	200	400	400
Total throughput (kg/h)	**5**	**5**	**10**	**10**

Table 3. Various TSG process parameters. Note that one of the tablets was produced with a high-shear granulator (HSG).

Figure 6 shows the Raman correlation map of the S4 formulation. Red spots indicate areas of high correlation for Raman spectra with that of loperamide hydrochloride. Loperamide hydrochloride is distributed evenly in the tablet but variations in particle size are evident. This suggests inhomogeneous particle size distribution of the drug substance. Larger crystals of loperamide hydrochloride were unable to break up in simethicone under the conditions of the process before being deposited on the carrier particles. Nevertheless, loperamide hydrochloride in liquisolid tablets was evenly distributed, as confirmed by the results of the uniformity of dosage units, which met the acceptance criteria required by the pharmacopeia.

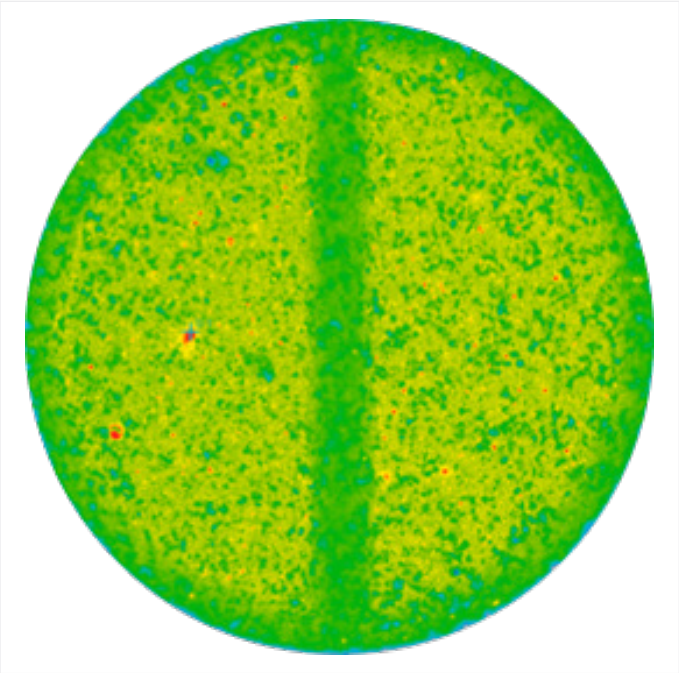

Figure 6. Raman correlation map showing the spatial distribution of loperamide hydrochloride; red sites are those with the highest, and blue sites are those with the lowest correlation of the Raman spectrum with that of loperamide hydrochloride.

In conclusion, Raman imaging is an enormously powerful analytical technique for evaluating the effect of the production process on the efficiency of simethicone sorption on the carrier, as well as the distribution of the individual components in tablets.

Acknowledgement

Special thanks to Daniel Zakowiecki, Markos Papaioannou, Peter Edinger, and Tobias Hess from Chemische Fabrik Budenheim KG, Krystyna Mojsiewicz-Pieńkowska and Krzysztof Cal from the Medical University of Gdansk, as well as to our colleague Annika Voelp from Thermo Electron (Karlsruhe) GmbH for collaboration and allowance to extract the results from the study “Towards the Continuous Manufacturing of Liquisolid Tablets Containing Simethicone and Loperamide Hydrochloride with the Use of a Twin-Screw Granulator”[1].

References

1. Zakowiecki, D.; Richter, M.; Yuece, C.; Voelp, A.; Ries, M.; Papaioannou, M.; Edinger, P.; Hess, T.; Mojsiewicz-Pieńkowska, K.; Cal, K. Towards the Continuous Manufacturing of Liquisolid Tablets Containing Simethicone and Loperamide Hydrochloride with the Use of a Twin-Screw Granulator. Pharmaceutics 2023, 15, 1265. https://doi.org/10.3390/pharmaceutics15041265
2. US Pharmacopoeia; General Chapter: Uniformity of Dosage Units <905>. In: USP/NF. Rockville, MD: USP; 2020. DOI: https://doi.org/10.31003/uspnf_m99694_02_01.