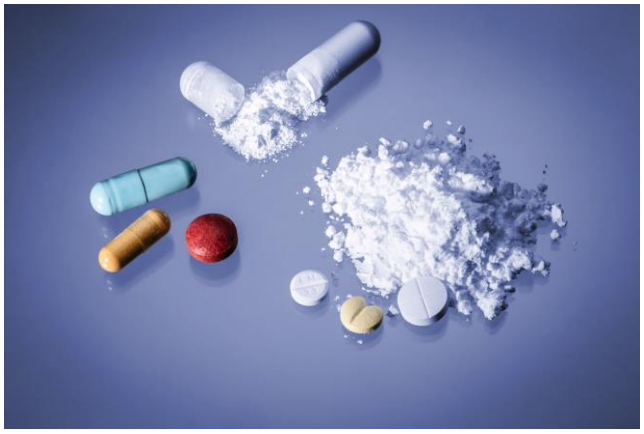
Identity Testing of Raw Materials using Raman Spectroscopy: Excipients

Relevant for: Pharma

Cora 5001 together with the pharma compliant Spectroscopy Suite desktop software is a fast tool for identity testing of excipients for pharmaceutical products. Method development and validation according to USP regulation is easily possible.



The pharmaceutical production industry is one the most heavily regulated markets in the world. From the delivery of raw materials to the packaging of final products the production processes need to be monitored according to legal requirements ensuring product quality and minimizing the risks for the patients in all parts of the world. The excipients used in the formulation, so the parts of the drug product that are not pharmacologically active, need to be tested among other things for their chemical identity as stated by international pharmacopeias and current GMP guidelines. [1], [2], [3] Here, fast and accurate methods are required to quickly assess whether a batch is fit for further use or needs to be rejected. Anton Paar's Cora 5001 Raman spectrometers together with the Spectroscopy Suite desktop software offer fast and reliable ID testing using algorithmic database matching. Method development and validation are straight-forward and easy to handle processes due to the intuitive user interface. As the software is fully compliant to CFR 21 part 11 according to FDA, data integrity and a complete audit trail are ensured.[4]

1 Excipients

Excipients are commonly referred to as the non-active part of a drug product. They are not pharmacologically active but not really inert components either as they serve different functions within a drug product. Among other things they may aid in manufacturing of the drug product, increase bulk or improve stability. Furthermore, they may enhance drug delivery and targeting, alter the pharmacokinetic profile of the drug product or enhance the products safety.[5], [6]

According to international pharmacopeias identity testing is required for every excipient used in drug production as stated in the respective chapters.[7], [8]

2 Requirements for ID Testing with Raman Spectroscopy according to USP

According to US Pharmacopeia chapter 197, Raman spectroscopy may be used for identity testing of raw materials such as excipients.[8] The following recommendations apply: the measurement device should be prepared for the measurement according to the manufacturer's recommendations and a performance check should be conducted prior to use. Spectra of sample and references should be collected using the same instrumental parameters. The resulting spectra are then compared qualitatively. Where available a USP reference standard should be used as reference sample.[7] The qualitative comparison can be conducted algorithmically using chemometric models.[9] The method has to be validated according to USP 1225.[10] For qualitative analyses the specificity and the robustness of the method have to be demonstrated during method validation.[9], [10]

Figure 1: Anton Paar's Cora 5001 Raman spectrometer series (left: Direct version; right: Fiber version).

3 ID Testing using Raman Spectroscopy

3.1 Experimental Setup

For ID testing of the excipients a Cora 5001 Direct Raman spectrometer with an excitation wavelength of 785 nm was used. The instrument is compliant to USP 858 and therefore perfectly suited for ID testing using Raman spectroscopy.[11] It was controlled via Anton Paar's Spectroscopy Suite desktop software which fully complies to CFR 21 part 11 according to FDA, ensuring data integrity.[4]

3.2 Method Development

The instrument was checked for correct calibration with the supplied System Suitability Test (SST) standard prior to use. As a first step to method development test runs were conducted for optimization of measurement conditions. The implemented autofocus and automatically determined exposure time render this process swift and hassle-free. The obtained parameters were saved in a method which was submitted, reviewed and approved by the responsible users. Subsequently, a good quality library spectrum of each reference substance was measured using the previously developed method and submitted for approval. After approval by the responsible lab manager the spectra were fit to be used in a spectral library.

3.2.1 Spectral Library Development, Publication and Approval

For each substance a library entry with the corresponding spectrum was created. The software offers the possibility to enter further information on the substance such as names or GHS symbols as well as a comment field for other relevant information. Subsequently, each substance entry and the whole library are submitted for approval. After approval the library is fit for use in an ID testing method.

3.2.2 ID Testing

An identification method is created using the same parameters as used for the measurements of the library spectra, as required by USP. The software offers to copy the method used to acquire the reference data and to add identification parameters for the intended analysis, therefore equality of the measurement parameters can be easily achieved. The new method is signed (submit, review, approve) as well by the responsible employees. Subsequently, samples of each API (see Table 1) were measured and identified.

Table 1: List of tested excipients.

Excipient	Substance class	Substance Number
Ethyl cellulose	Polysaccharide	A1
Hydroxypropyl cellulose	Polysaccharide	A2
Microcrystalline cellulose	Polysaccharide	A3
Fructose	Monosaccharide	B1
Glucose	Monosaccharide	B2
Lactose Monohydrate	Disaccharide	B3
Maltose Monohydrate	Disaccharide	B4
Saccharin	Benzothiazole	B5
Sucrose	Disaccharide	B6
Acetone	Ketone	C1
Aspartame	Ester of dipeptide	C2
Benzaldehyde	Aldehyde	C3
Benzyl alcohol	Alcohol	C4
Ethanol	Alcohol	C5
Ethyl acetate	Ester	C6
Glycerin	Polyol	C7
Isopropanol	Alcohol	C8
Methanol	Alcohol	C9
Adipic acid	Acid	D1
Ascorbic acid	Acid	D2

Table 2: HQI Matrix showing specificity and robustness (triple measurements) of ID testing method for substance group A (cellulose derivates).

	A1	A2	A3
A1	99.04	13.53	72.78
A2	18.64	99.68	16.32
A3	72.13	13.27	99.40

Table 3: HQI Matrix showing specificity and robustness (triple measurements) of ID testing method for substance group B (sugars).

	B1	B2	B3	B4	B5	B6
B1	99.87	4.21	10.21	4.04	0.01	4.79
B2	4.19	99.90	36.63	51.50	1.18	29.80
B3	8.95	37.71	99.53	44.80	0.91	20.37
B4	3.76	51.24	44.28	99.84	0.07	24.59
B5	0.02	1.15	0.74	0.08	99.97	0.44
B6	5.18	27.74	18.33	23.54	0.38	99.18

Table 4: HQI Matrix showing specificity and robustness (triple measurements) of ID testing method for substance group C (solvents)

	C1	C2	C3	C4	C5	C6	C7	C8	C9
C1	99.99	0.12	0.15	0.45	0.13	1.57	0.01	0.55	0.04
C2	0.10	99.88	13.84	39.68	0.19	0.21	0.06	5.04	5.04
C3	0.14	13.25	100.00	40.61	0.64	0.01	0.44	0.05	0.19
C4	0.45	38.12	40.80	99.99	0.09	0.46	0.11	1.01	6.12
C5	0.14	0.21	0.63	0.09	99.99	2.76	22.68	2.43	13.41
C6	1.57	0.21	0.01	0.46	2.76	99.99	11.21	1.84	1.81
C7	0.01	0.07	0.43	0.12	22.75	11.28	99.99	9.34	17.65
C8	0.53	4.90	0.06	1.04	2.32	1.82	9.35	99.98	1.52
C9	0.04	4.94	0.20	6.12	13.53	1.81	17.41	1.62	99.99

3.3 HQI Matching Algorithm

For the comparison of reference and sample spectra the Anton Paar Spectroscopy Suite offers an HQI matching algorithm. The results of the algorithmic matching lie between zero for no correspondence and 100 for identical spectra.

By defining a suitable HQI threshold the identification or verification of substances can easily be achieved.

4 Results and Method Validation

Tables show the resulting matches of each sample against each reference spectrum for the respective sample groups of excipients for cellulose derivates (Table 2), sugars (Table 3) and solvents (Table 4) using the HQI (Hit Quality Index) matching algorithm. It is clearly visible that the substances are identified correctly with an HQI threshold of 95 for the spectral range of 300-2300 cm^{-1}. The specificity of the method is clearly visible when comparing the spectra of structurally very similar substances such as different cellulose derivates. The HQI difference is at least 26 and therefore the substances are well separable with the implemented algorithm. Figure 2 shows the Raman spectra obtained for the different cellulose derivates: ethyl cellulose, hydroxypropyl cellulose and microcrystalline cellulose. The Figure illustrates again the discrimination power of Raman spectroscopy. Even though the compounds are structurally very similar they can easily be distinguished by their spectral fingerprint.

Figure 3 shows the Raman spectra of different solvents. Since these are usually quite small molecules the spectral discrimination is even better. The HQI values are more than 48 apart.

Finally, Figure 4 shows different sugars. The monosaccharides glucose and fructose are isomers of each other. The disaccharides sucrose, maltose and lactose are even diastereomers of each other. The Raman spectra differ substantially which is also reflected in the large difference in HQIs of more than 59.

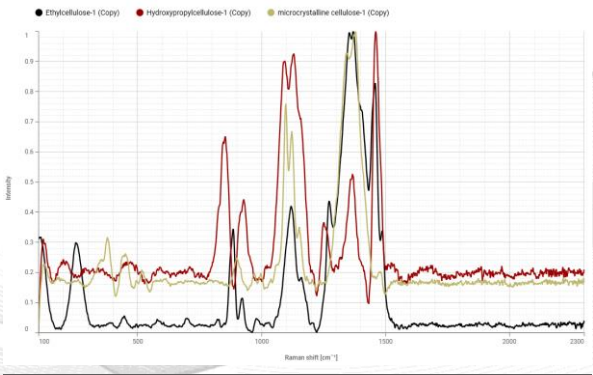


Figure 2: Raman spectra of different cellulose derivates as shown in the processing menu of the Anton Paar Spectroscopy Suite software. Raman spectra have been normalized to the highest peak.

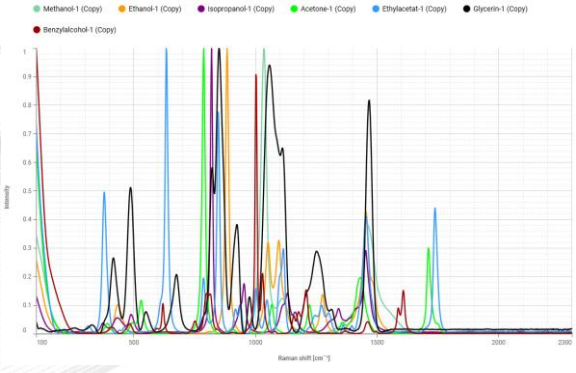


Figure 3: Raman spectra of different solvents, esters and ketones as shown in the processing menu of the Anton Paar Spectroscopy Suite software. Raman spectra have been normalized to the highest peak.

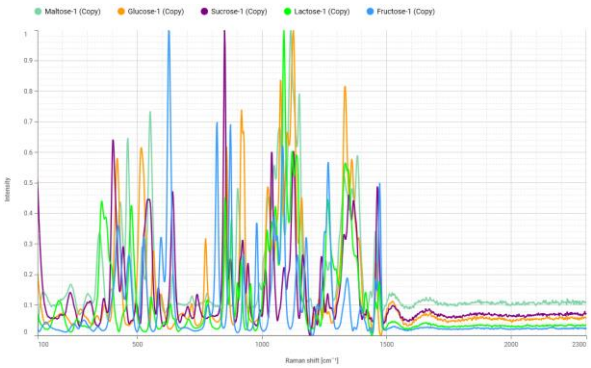


Figure 4: Raman spectra of different sugars as shown in the processing menu of the Anton Paar Spectroscopy Suite software. Raman spectra have been normalized to the highest peak.

Measurements were performed in triplicate to also evaluate repeatability. Standard deviations varied between 0.00002-0.47 of the HQI within the respective sample groups. It is recommended to validate a method by measuring spectra on different days and by different instrument operators. After validation the method is fit for use in the production.

5 Conclusion

Raman spectroscopy using Anton Paar's Cora 5001 Raman spectrometer together with the Spectroscopy Suite desktop software speeds up identity testing for a plethora of excipients including structurally very similar ones. Validation of the method demonstrates specificity and robustness of the procedure and is established equally fast as the test measurements themselves.

6 References

[1] USP. Oral Drug Products – Product Quality Tests <2> In: USP-NF. Rockville, MD: USP; Oct 12, 2021.
DOI: https://doi.org/10.31003/USPNF_M3211_05_01

[2] USP. Topical and Transdermal Drug Products – Product Quality Tests <3>. In: USP-NF. Rockville, MD: USP; Oct 12, 2021.
DOI: https://doi.org/10.31003/USPNF_M4033_05_01

[3] 21 CFR part 210. Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs; General. U. S. Food and Drug Administration, retrieved Nov 11, 2021.
https://www.ecfr.gov/current/title-21/chapter-I/subchapter-C/part-210

[4] 21 CFR part 11. Electronic records; electronic signatures. U. S. Food and Drug Administration, retrieved Oct 12, 2021.
https://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=11&showFR=1

[5] Pramanick et al., *Pharma Times*, **2013**, *45*, 3.

[6] The International Pharmaceutical Excipients Council (IPEC) and the Pharmaceutical Quality Group (PQG), *The Joint Good Manufacturing Practice Guide. For Pharmaceutical Excipients*, **2017**. [Online]. Available at: https://www.ipec-europe.org/uploads/publications/20170517-ipec-pqg-gmp-guide-final-1536242212.pdf, retrieved Dec 15, 2021.

[7] USP. Identification Tests – General <191>. In: USP-NF. Rockville, MD: USP; Oct 12, 2021.
DOI: https://doi.org/10.31003/USPNF_M98940_09_01

[8] USP. Spectroscopic Identification Tests <197>. In: USP-NF. Rockville, MD: USP; Oct 12, 2021.
DOI: https://doi.org/10.31003/USPNF_M98947_05_01

[9] USP. Chemometrics <1039>. In: USP-NF. Rockville, MD: USP; Oct 26, 2021.
DOI: https://doi.org/10.31003/USPNF_M2345_02_01

[10] USP. Validation of Compendial Procedures <1225>. In: USP-NF. Rockville, MD: USP; Oct 26, 2021.
DOI: https://doi.org/10.31003/USPNF_M99945_04_01

[11] USP. Raman Spectroscopy <858>. In: USP-NF. Rockville, MD: USP; Oct 12, 2021.
DOI: https://doi.org/10.31003/USPNF_M8188_02_01

Contact Anton Paar GmbH

Tel: +49 511 40095-0 | www.anton-paar.com

application-optotec@anton-paar.com