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RAMAN SPECTROMETRY AND MULTIVARIATE METHODS FOR DEVELOPMENT OF PHARMACEUTICAL TECHNOLOGY

Summary of PhD Thesis

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1. Introduction

A rapid spreading can be observed in the use of Raman spectrometry. The increasing importance of the technique lies in the fact that information can be collected about a sample in a contactless manner and without changing of the sample structure. The pharmaceutical industry also recognized that the use of Raman spectrometry makes it easy to characterize the active ingredients and the excipients.

In the pharmaceutical industry over the last decade, two important directives have come to the fore. The implementation of these issues will speed up the spread of continuous production technologies. With the principle of Quality by Design (QbD), the most important parameters of the processes are identified and a control strategy is developed allowing the change in the quality of the intermediate or the final product between certain limits using risk assessment. Where it is needed to use the design of experiment and study the design space. The concept of process analytical technology (PAT) can ensure the quality of the product along a process line by constant monitoring and control. This will enable the replacement of the cost, time and energy-intensive end product tests used in batch processing. However, until the routine use of the new principles development is needed especially for the pharmaceutical industry in the next years.

By Raman spectrometry, qualitative, quantitative - excellent time and spatial resolution – data can be obtained from pharmaceutical samples. When unknown or partially unknown samples (counterfeit, illicit or original drugs) are explored, a number of issues can be decided by developing correct, accurate evaluation procedures.

Increasing the efficiency of the methods used for quantitative analysis is particularly important if a monitoring or a feedback on critical parameters have to be implemented.

Instrumental analytical techniques provide a huge amount of data of which requires appropriate handling to extract and process relevant information. This is particularly vigorous for Raman spectrometric techniques, especially for *chemical mapping*, at which thousands of spectra can be generated from time to time. The studied analytical signals can be treated effectively with *multivariate data analysis*, also known as *chemometric method*s.

We intended to develop these methods so that that they will be well-utilized at several levels of pharmaceutical technology. The applicability of Raman spectrometry was

to be improved along the following major directions:

- Characterization of spatial distributions in pharmaceuticals with unknown compositions to detect the number of the components and explore the used manufacturing technology. It was required that the procedure for **characterizing the homogeneity of Raman maps** will be also generalized to be suitable for quantitative **comparison of different manufacturing technologies**.
- It is a key issue in various pharmaceuticals to **determine the amorphous-crystalline fractions**. It was important to ascertain whether selective spectrum ranges could be selected that is suitable for quantitative determination of amorphous and crystalline active ingredients. Furthermore the study of the partial amorphous active ingredients could be achieved in solid dispersions, when the API cannot be produced in pure amorphous form.
- Pure spectra can be obtained from the mixed spectra by some **self-modelling curve resolution methods**. We have attempted to adapt a new method for **estimating the number of components** to be set up in these processes.
- Evaluation and critical **comparison of the novel multivariate methods** (for quantitative determination and the efficient regression) not used so far in Raman spectrometry. In addition, it was worthwhile to examine that the quantification methods and efficient models how can assist to real-time monitoring of quality helping the industrial realization of PAT principles.
- Development of a system, that is suitable for prepare **chemical reactions** in accordance with the PAT requirements, was in center of our researches. In this case the control of the **critical parameters** was required with a proper **in-house developed feedback** strategy.

2. State of art

The vibrational spectroscopic techniques have great importance in theoretical and practical issues. With chemical imaging the local analysis can be performed. Various new details can be observed by the microscopic investigations, which would otherwise remain hidden with the macroscopic (bulk) analytical methods[1],[2]. Not only the field of

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chemical mapping has been progressing over the past decade[3], but the pharmaceutical industry is beginning to recognize the importance of PAT[4]. One of the promising tools can be the use of the Raman spectrometry through the probe in the reflection or transmission mode[5], which allows for real-time analysis[6]. However, these advanced analytical tools can be made really effective when measured data is processed using multivariate data analysis methods.

Spatial information (such as the determination of heterogeneity) available through Raman mapping is increasingly needed in the pharmaceutical industry. Not only the appropriate content uniformity of an active ingredient can be investigated, but it may also be necessary to analyze samples of unknown compositions (*e.g.* counterfeit drugs). Some conclusions can be made to the production techniques based on homogeneity. These provide important results for both original and generic manufacturers. In a distribution map, the groups of adjacent pixels are called macropixels. By increasing the size of the macropixels gradually, larger pixels can be also created. Meanwhile, homogeneity can be investigated in each step. This principle is called macropixel analysis. There are two forms known: *discrete-level tiling*[7] (DLT) and *continuous-level moving block*[8] (CLMB). Nobody has ever used them and compared them to distinguishing different manufacturing technologies.

Amorphous and crystalline drug examinations should also be made in cases where there is insufficient information for the drug products or when the amorphous substance cannot be prepared in pure form. Such studies have not been performed yet.

In the case of an unknown tablet, it is necessary to know the number of spectral components to be used for the different spectrum processing methods[9] (such as MCR-ALS). However, there are no adequate procedures known to this purpose. In this dissertation, we have attempted to develop a variable clustering method[10] based on a new approach that has never been applied to Raman maps.

The use of chemical mapping for quantitative analysis would also be niche in the pharmaceutical industry. With common univariate evaluation and CLS modeling, the right precision cannot be achieved. Therefore, chemical maps containing real concen-

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trations can only be created with a new approach. For this purpose, we used variable-selection methods and regression methods for handling non-linearity less or not used at all.

Transmission Raman spectrometry offers a new possibility of rapid control of tablets, but it can only be sufficiently accurate if novel methods for quantitative determinations.

Investigating important processes in the pharmaceutical industry can only become really effective if the spectra are not only interpreted, but we react for the calculated numbers by intervening. Prior to this PhD work, no documented experiments have been carried out on the control of chemical reactions.

3. Experimental and evaluation methods

The Raman spectrometry is the core technique of the dissertation. It was applied to each topic. The experiments with chemical imaging were carried out on various powder mixtures or tablets using a LabRam Raman spectrometer manufactured by Horiba Jobin Yvon. A probe connected to the spectrometer enabled to monitor and control the reaction. Transmission Raman measurements of the polymorph blends filled in capsules were performed with the AccuRa type instrument of the same company. The spectra were preprocessed with any data preparation method before each evaluation. This consisted mostly of baseline correction on spectra or normalization correcting of the focusing uncertainty during the measurement of the spectra (with Labspec 5.41 software). In addition, several methods were used, which were optionally optimized by comparing different methods (PLS Toolbox 6.5-8.0).

Some tablets were produced in a non-disclosure manner due to industrial property rights, in which the distribution maps were tried to determine using VARCLUS variable-clustering and MCR-ALS methods. Further samples for examination of different manufacturing technologies were prepared using the following technologies: direct compression (Fette EX-1), high-shear granulation (Pro-C-ept 4M8) and fluidized-bed (Glatt GCPG-1) granulation and melt extrusion (HAAKE Minilab) and electrospinning. Raman maps made from these were quantified by our own developed macropixel analysis (algorithm created in Matlab) to compare the distributions of the drug.

Raman maps of amorphous and crystalline active substances in a tablet formulation (not detailed for industrial property right protection) were treated with VARCLUS and

then evaluated by CLS modeling. Amorphous solid dispersions of itraconazole with different excipients were generated by high productivity electrostatic spraying (HSES) and spraying drying (SD) in our research group. The collected Raman maps were evaluated by MCR-ALS for comparability of the samples.

For quantitative analysis of solid dispersions, samples containing caffeine model API and polylactic acid co-glycolic acid excipient were prepared by spray drying (Pro–C-Ept MicroSpray) with eleven different compositions. Samples containing spectrally similar components were also generated from two polymorphs of carvedilol and mixtures of imipramine, starch and cellulose in both cases with nineteen different compositions. Numerous univariate and multivariate regression methods were tested by comparing the errors of cross-validation derived from calibration sets and the predictive errors for the validation sets.

To determine the polymorph named ‘C’ composition in real time, different types of capsules were filled with 23 different forms of Forms A and B. In this case, univariate and CLS regression were compared with PLS, PCR, PLS-GA and SVR models while spectrum acquisition times have been decreased.

To monitor and control a chemical model reaction, a glass-based tank reactor, created in our research group, was used, which was equipped with special dosing, cooling, heating and mixing unit, temperature and pH meter. The system was coupled to a PLC unit. Capability for measurements by Raman probe was tried to develop in order to perform real-time control.

The aquisition and basic evaluation of the spectra (visual comparison, baseline correction, normalization) was performed with the LabSpec 5.41 (Horiba) program as well as the CLS modeling with the reference spectra and the detection of concentration maps. Most of the chemometric calculations and the more complex data preparation methods were performed with the latest version of the Matlab (7.9.0-8.5.0) program (Mathworks) and its plug-in PLS_Toolbox (Eigenvector Research) program (6.5-8.0). The macropixel analysis was used in a Matlab script as the SAM-OP method was implemented on a Matlab interface. The VARCLUS procedure was used as Tanagra 1.4. Software plugin Excel extension. The SRD method was also used with the Excel VBA macro downloadable from online source. To display the estimated spectra and concentrations, the results were converted in Microsoft Excel into a text file formed, that can be processed by the LabSpec program. Univariate statistical calculations were also performed with Matlab, Excel programs.

4. Results and discussion

4.1. Analysis of component distributions in pharmaceuticals

The distribution of the components in solid dosage forms was characterized by Raman mapping. For this purpose, the Raman microscope is suitable with collecting hundreds or thousands of spectra. A new method has been developed for making distribution maps in cases where the spectral components of the tablet are not fully known (no proper reference) and the manufacturing technology of the tablet has to be determined (*e.g. for generic development*). Variable clustering was used to determine the number of components that can be calculated by the curve resolution methods. Then the spectra of the components could be estimated. The composition was determined with the Raman-intensity correction of CLS modeling. Finally, by correlating the distribution of the components, we could have predicted technological steps prior to tableting.

There are few examples for evaluating homogeneity of Raman maps by macroscopic analysis in the literature. This method has been further developed to make it possible to numerically compare different manufacturing technologies and set up an order of homogeneity based on Raman maps. The improved method distinguished the classical manufacturing techniques from the finely distributed solid dispersion techniques and showed a substantial difference even among these types of dispersions.

4.2. Determination of amorphous crystalline fraction in pharmaceuticals

The determination of the stability of amorphous ingredients and the determination of the amorphous crystalline fraction in certain sample is an important, but challenging analysis in the pharmaceutical industry. The formulation should be retained for the expiration date.

A procedure has been developed for evaluating solid phase Raman spectrometric measurements. We investigated the stability of the amorphous crystalline drug fraction formed in a product. First, a selective spectral range has been determined by calculations for optimal evaluation, and then CLS modeling was used on this map, taking into account that the active substance content changed from point to point.

Another problem that has not yet been studied is that Raman spectra of solid dispersions generated with various excipients how can be evaluated when the difference

between the amorphous and crystalline spectra is differently influenced by the signs of the excipients. A methodology has been proposed this way using an MCR-ALS method. From the extracted information the stability of the amorphous drug can be easily interpreted.

4.3. Estimation of the number of components in pharmaceutical samples

For the determination of pure component spectra from the Raman maps, numerous self-modeling curve resolution methods are used. Mostly, these methods require the starting component number. Estimation of this number is in the focus of research. The method based on the variable clustering could be adapted for this purpose, which made possible to specify exactly how many components can be expected when examining a Raman chemical map. In unknown cases, the method showed the number of major components very well. The formed groups from variables clearly mirrored the typical peaks of the particular components, which could be confirmed with SRD method. It was also pointed out that if a spectrum library is available, the number of minor components - that can be extracted - can also be increased. This was demonstrated successfully in a much more complex system than an average tablet.

4.4. Quantitative determination based on Raman spectra using regression methods

Raman spectra provide not only qualitative, but quantitative information as well. However, it is often not enough to use the simplest regression models to determine it precisely. Certain difficulties can occur at quantifying a single Raman map. On the one hand, our experience shows that the normalization of the spectra and the simpler univariate or CLS evaluations give strongly distorted result when significant difference exists between Raman activities of the active substance and the excipient, while, on the other hand, for very similar spectra the evaluation requires the use of advanced regression methods. Maps containing real concentrations could be created by applying systematically selected intervals or genetic algorithm-based variable selection. Distortion caused by PLS mode to calculate noisy spectra was also eliminated. To distinguish similar spectra of polymorphic impurities and different, but chemically low variants of excipients, it was particularly important to improve the quality of accurate quantitation. In these cases, methods used to handle nonlinearity of regression models (LWR, pPLS,

SVR) led to best results (Figure 1). We therefore proposed using the analytical method developed on the basis of these methods.

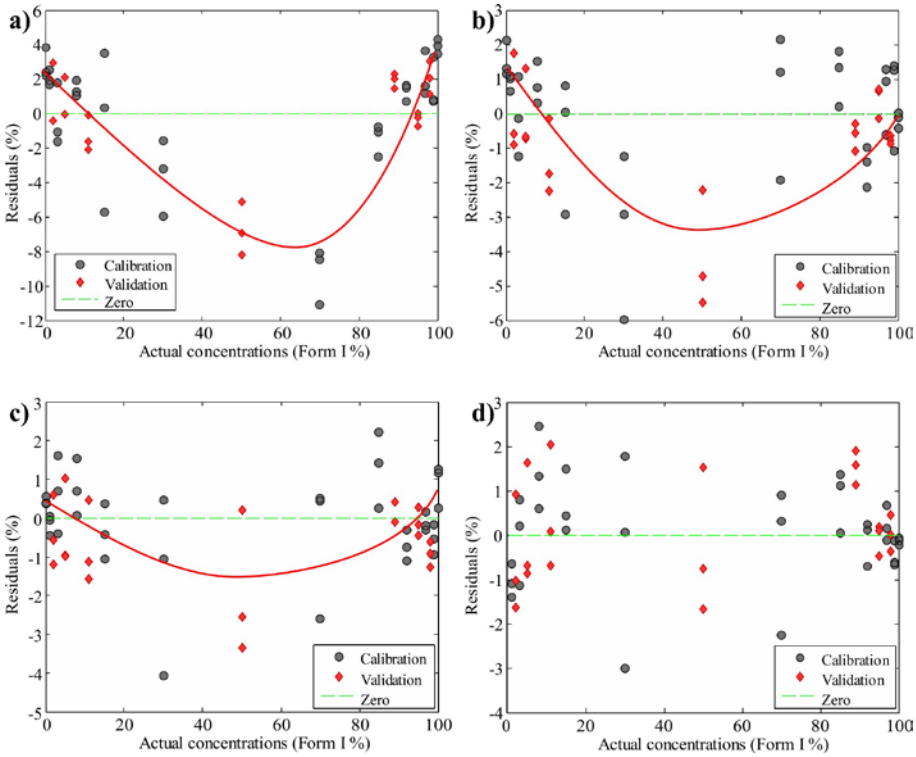

Figure 1 Residuals of regression models on carvedilol polymorphs
a) CLS, b) PLS, c) iPLS és d) pPLS

Finally, the applicability of transmission Raman spectrometry was examined for nearly real-time measurements required in the industrial practice of PAT methods. Advanced regression models have been found to compensate the reduction of signal to noise ratio at shorter measurement times.

4.5. Development of Raman-based feedback control for chemical reactions

Before this work chemical reactions have not yet been controlled in real time using Raman method. In this field a breakthrough was intended to achieve, therefore we demonstrated with a model reaction how to control a dangerous reaction by administering the dosage (as a critical parameter) by using a suitable chemometric method. The MCR-ALS method was used to produce a reference spectrum for the spectral monitoring of the non-preparable intermediate providing a more accurate control. At the slightly alkaline pH, a PI control was made by monitoring spectral concentrations in real-time for the addition of the reagent (Figure 2).

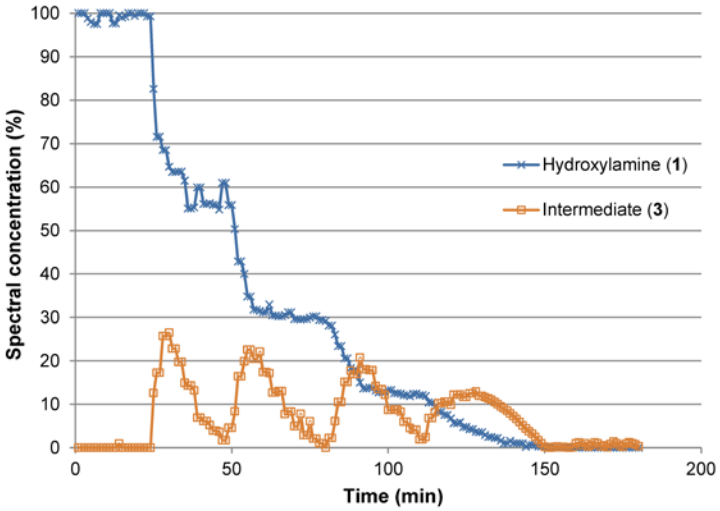

Figure 2: Inline calculated spectral concentration profiles of reactant (**1**) and intermediate (**3**) at pH 9.5 in oximation

5. Theses

1. It was proposed to apply a modified index (corrDHI) for quantifying the distribution of components of pharmaceuticals by macropixel analysis of Raman maps created by CLS or MCR-ALS. Various manufacturing technologies are thus comparable and distinguishable exactly so that the different procedures can be accurately identified by chemical maps. [I]

2. New evaluation methods have been worked out for testing the stability of amorphous form of various active ingredients and the determination of the amorphous crystalline fraction by Raman mapping in nanofibers and tablets. The spectral changes in the crystallization of various drugs and the presence of excipients required different preparation methods tailored to the product. The approaches can be used to investigate other active ingredients of similar behavior as protocols. [II, III, X]

3. Variable clustering method was applied on Raman maps for the first time to estimate the number of components in the sample and to select selective bands. The efficacy of the process was analyzed from simpler, low-component tablets to the complex multi-component powders. It was proved that the sum of the ranking differences (SRD) is suitable to validate the results of the clustering. [IV, V]

4. Multivariable regression models based on Raman spectrometry were improved by variable selection methods, by which real concentration distributions could be visualized on Raman maps of spray-dried systems for the first time. It was shown that the estimation errors from the noise of the spectra can be corrected by variable selection. [VI]

5. Methods for handling non-linearity, which were previously unused in Raman spectrometry, could be applied for the quantitative modeling of systems with very similar spectra. Quantitative analysis of pharmaceutical polymorphs and tablets has resulted in more precise concentration determinations. [VII, IX]

6. Quantitative analysis in transmission Raman spectrometry was performed by variable selection based on a genetic algorithm for short measurement times, so that the results can be applied to continuous in-process controls.

7. A Raman-based feedback control was implemented in an organic synthetic reaction for the first time. In an oxidation model reaction, the resulting non-isolated intermediate was separated from the other components by spectral analysis using a MCR-ALS method and then a secure control was constructed through the quantitative model based on the chemometrically produced spectral signal. [VIII]

6. Application possibilities

The procedures and problems in this PhD thesis are wide-ranging, but all the time, the more accurate examination of the pharmaceuticals and the better understanding of the technological steps led the experiments. Spectrum evaluation methods were introduced that could generate new interesting surplus content for generic developers when examining reference formulations (for examination of manufacturing technologies or distribution). Discovery of unknown or partially unknown preparations will also be easier. Our results in the field of quantitative determination in Raman spectrometry can be used in chemical maps and mainly in continuous pharmaceutical production. Raman based procedures can be further improved by the tools we created. Last but not least, the first Raman-based control of chemical reactions demonstrated that spectral data can be useful not only for process monitoring but also to intervene processes leading them to a favorable direction.

7. List of related publications

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