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INFRARED SPECTROSCOPIC METHODS FOR PHARMACEUTICAL QUALITY CONTROL

PhD theses booklet

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1. Introduction and objectives

Due to the development of biotechnological processes in the pharmaceutical industry and the tightening of regulatory requirements for end products, the concept of Quality by Design (QbD) and the use of Process Analytical Technology (PAT) have become widespread in recent decades. At the same time, there has been a growing need to develop and use high-throughput analytical methods.

Vibration spectroscopic methods enable robust and cost-effective pharmaceutical production, including fast, non-destructive, and automated analytical techniques, such as near-infrared (NIR) and Fourier transform infrared (FT-IR) spectroscopy. The topic of my PhD work is the development of infrared spectroscopic methods as a fast and non-destructive alternative at certain stages of the pharmaceutical quality control process. The developments have focused on the qualitative and quantitative analysis of raw materials, process aids and end products. These are currently classified using costly and time-consuming preparative methods or separation techniques. In addition, the experiments in each case highlight a vital issue for spectroscopic method developments.

The objectives of my PhD work were the following:

1. Building appropriate calibration models using near-infrared spectrophotometers with different optical constructions (dispersion, Fourier transform, diode array) to monitor the active pharmaceutical ingredient concentration in transdermal gel formulations using transflection mode and partial least squares regression.
2. Measurement of preparative chromatographic media used for protein purification with attenuated total reflection (ATR) measurement technique in the mid-infrared range to develop a method for characterization and classification of chromatography media without sample preparation.
3. Comparison of the efficiency of classification techniques (linear discriminant analysis, partial least squares discriminant analysis, soft independent modeling of class analogies) and selection of the optimal method using experimental and simulated near-infrared spectra of heat-treated mammalian cell culture medium powders and creating a strategy of model development based on simulated spectra.

2. Background

QbD is a systematic approach to development based on scientific findings and quality risk management, enabling targeted product quality through process understanding and control. One of the tools for its implementation is the PAT, which is a system for planning, analyzing and controlling production and helping to ensure the quality of the final product by controlling critical quality and performance characteristics in time. Scientific reports and regulatory recommendations from the last few decades well reflect the excellent application of vibrational spectroscopic methods (including NIR and Raman spectroscopy) in manufacturing plants using PAT, QbD or Industry 4.0 approaches, including in the pharmaceutical industry.[1]

Considering the Q11 guidelines of the International Conference on Harmonization, when developing a process based on the QbD principles, the risk analysis should also include examining starting materials, excipients, and intermediates to identify critical components for the quality of the final product.[2] Furthermore, it is necessary to monitor the physical or chemical properties of the components considered to be essential, and in this case, it is advantageous to use fast, high-throughput and cost-effective techniques. Therefore, the aims of developments presented in my PhD work were the analysis of mammalian cell culture medium powder (raw material), preparative chromatographic media (process aid) and transdermal gel formulations (final product), which are currently classified using costly and time-consuming procedures.

The control of nutrient solutions used in mammalian cell fermentation is most often performed based on cell culture assays and the determination of critical components by liquid chromatography, which further increases the unit cost of production. Recommendations from the U.S. Food and Drug Administration on biotechnology productions support introducing innovative data management tools and PAT techniques.[3] As a result, in addition to traditional qualification methods for monitoring nutrient powders, spectroscopic techniques, including NIR spectroscopy, are increasingly being used to monitor the variability of raw materials and to detect changes in their long-term storage, proving that NIR combined with reliable and cost-effective data analysis in the release processes of substances entering the fermentation technology. [4]

[1] T. Eifert et al. (2020) *Analytical and Bioanalytical Chemistry* 412: 2037–2045.
[2] ICH Harmonized Tripartite Guideline (2012) Development and Manufacture of Drug Substances Q11
[3] E.K. Read et al. (2010) *Biotechnology and Bioengineering* 105: 276.
[4] C. Hakemeyer et al. (2013) *Biotechnology Journal* 8: 835–846.

Isolation of the active ingredient from other components in the fermentation broth are essential in biotechnological drug production. A crucial process aid in protein cleaning is the preparative chromatographic media, which may have different physical and chemical properties depending on the purpose and conditions of the separation method (e.g. affinity, anion exchange, cation exchange, hydrophobic interaction chromatography). These materials' characterization and quality control are commonly performed based on small-scaled measurements using a packed column, which is lengthy, requires a valuable fermentation broth containing the active pharmaceutical ingredient, and provides little information about the cause of any discrepancies or non-conformities.[5] For these reasons, there is a need to develop a more straightforward analytical method that can reduce both sample requirements and analytical response times. Spectroscopic techniques such as FT-IR, NIR, ultraviolet, fluorescence and Raman spectroscopy are also suitable to examine chromatographic media.[6] Examples in the literature are mostly NIR, FT-IR and Raman spectroscopic measurements, which are preceded by lengthy sample preparation requiring at least 12 hours with filtration, washing and drying steps,[7] so the development of a measurement method without sample preparation would be a significant step forward.

In the quality control of semi-solid dosage forms, such as transdermal gel products, spectroscopic methods are mostly used for qualitative analysis, although spectroscopic techniques, including NIR or Raman spectroscopy, are also suitable for the quantitative measurement of these formulations.[8] Publications aimed at quantitative analysis differ in the type of optical arrangement used and the sample handling technique used to perform the measurements. Performing a series of experiments involving several device types could provide a complete picture of the extent to which the optical arrangement affects the NIR-based quantitative analysis of transdermal gels.

[5] A.T. Hanke M. Ottens (2014) *Trends in Biotechnology* 32: 210–220.
[6] M. Rüdt et al. (2017) *Journal of Chromatography A* 1490: 2–9.
[7] M. Andersson, K.G. Knuuttila (2002) *Vibrational Spectroscopy* 29: 133–138.
[8] M. Blanco et al. (2008) *European Journal of Pharmaceutical Sciences* 33: 409–414.

3. Materials and methods

3.1. Samples

Transdermal gel formulation samples (TG): sample series of two formulations with two active pharmaceutical ingredients (API I and API II).

Formulation I: API I content between 1.0% and 3.0% (w/w), 9 calibration levels.

Formulation II: API II content between 0.5% and 2.0% (w/w), 11 calibration levels.

Preparative chromatography media samples (CM): samples of 42 batches from 22 different preparative chromatographic media formulations.

Support matrices: agarose, methacrylate, poly(styrene-divinylbenzene), porous glass.

Surface functionalities: Protein A, quaternary amine, N-benzyl-N-methylethanolamine, amine, sulfonate, sulfopropyl, sulfoisobutyl, phenyl, butyl, carboxyl, multimodal.

Medium powder samples (MP): PowerCHO-2 medium powder (Lonza, Walkersville, MD, USA) developed for Chinese hamster ovary cell lines after heat treatment according to a two-factor three-level full factorial design.

Heat treatment temperature: 30 °C, 50 °C, 70 °C

Duration of heat treatment: 1 h, 7 h, 13 h

3.2. Infrared spectra acquisitions

The measurements presented in my PhD work were performed in two regions of infrared light (mid- and near-infrared) using three instruments with dispersive (DS), Fourier transform (FT) and diode-array (DA) optical arrangement (*Table 1*).

Table 1. *List of infrared spectrophotometers used in each series of experiments.*
(TG: transdermal gel formulation; CM: chromatographic media; MP: medium powder)
✓ *: measurements presented in the dissertation that provide successful measurement results.*
× *: measurements tested but not presented.*

Region	Optical arrangement	Instrument	Experiment		
			TG	CM	MP
Mid-infrared (IR)	FT (ATR)	*Spectrum 400* *	×	✓	×
Near-infrared (NIR)	DS	*Foss NIRSystems 6500* †	✓	×	✓
	FT	*Spectrum 400* *	✓	×	✓
	DA	*Perten DA 7250* ‡	✓	×	

* PerkinElmer, Waltham, MA, USA
† Foss NIRSystems, Silver Spring, MD, USA
‡ Perten Instruments, Hägersten, Sweden

The few samples available made it difficult to develop and optimize spectroscopic methods. Therefore, using the *mvtnorm* software package of the open-source *R* programming language (version 3.3.1, R Foundation for Statistical Computing, Vienna, Austria), I created simulated spectra based on the measured absorbance spectra on each device to facilitate robust model building and statistical decision making.

3.3. Data analysis

For the mathematical pretreatment of the spectra, second ordered derivatives and baseline correction were used (Table 2). Qualitative and quantitative analyzes were performed using the multivariate data analysis methods shown in Table 3.

Table 2. *List of mathematical pretreatments used in each series of experiments. (TG: transdermal gel formulation; CM: chromatographic media; MP: medium powder)*

Type of pretreatment	**Method**	**Experiment**		
		TG	**CM**	**MP**
Baseline correction	standard normal variate (SNV)	✓	✓	
	multiplicative scatter correction (MSC)	✓		
Second ordered derivatives	gap-segment method	✓		✓
	Savitzky−Golay method	✓		

Table 3. *List of multivariate data analysis methods used in each series of experiments. (TG: transdermal gel formulation; CM: chromatographic media; MP: medium powder)*

Purpose	**Method**	**Study**		
		TG	**CM**	**MP**
Pattern recognition	principal component analysis (PCA)		✓	✓
Classification	linear discriminant analysis combined with PCA (PCA-LDA)			✓
	partial least squares discriminance analysis (PLS-DA)			✓
	soft independent modeling of class analogy (SIMCA)		✓	✓
Regression	partial least squares regression (PLSR)	✓		

4. Results

4.1. Methods for determination of active pharmaceutical ingredient in transdermal gels

Using NIR spectrophotometers with three optical constructions, transdermal gel samples containing two different active ingredients were measured. The difference between the two formulations was observed in the 1675-1825 nm and 2150-2400 nm regions of the DS and FT spectra and the 1150-1250 nm region of the DA spectra.

The relationship between the spectra and the API concentration of the formulations was performed by PLSR analysis, and the selection of the appropriate mathematical pretreatment was performed based on the RMSEC and RMSECV results provided during the PLSR. Therefore, it can be concluded that the calibration accuracy of PLSR based on the NIR spectrum is greatly influenced not only by the composition of the transdermal gel formulation but also by the type of the used NIR spectrophotometer. The DA device shows the best results for these formulations (*Table 4 and 5*). Furthermore, the regression coefficients of the models proved that the estimation ability of these regression models is related to the API's vibration peaks.

PLSR models based on simulated spectra were used to confirm the results of the calibrations. In the case of DS and DA, there were no significant differences between the results of the models based on the spectra of the original and the simulated data set ($p = 0.05$). Moreover, the performance indices of the FT models show a relevant variance, which may be due to the higher variability of the FT spectra.

According to the regulations of the European pharmaceutical authority, the maximum acceptable deviation in the API content of the final products shall not exceed ±5% at the time of manufacture.[9] The United States Pharmacopeia regulations also state that variation in a quality attribute cannot exceed ±10% from the target label claim.[10] When DA based RMSECV values of 0.040% and 0.144% for Formulation I and Formulation II are converted to relative errors (RMSECV divided by the target value of API content), the results are 1.3% and 7.2% for Formulation I and Formulation II, respectively, so DA calibrations of both formulations correspond to the USP requirement, and Formulation I also conforms to the European requisite.

[9] C.T. Ueda et al. (2009) *Pharmacopeial Forum* **35**: 750–764.
[10] Directive 2001/83/EC. OJ L 311, November 28, 2001.

Table 4. *The PLSR results for the raw spectra and mathematically pretreated dispersive (DS), Fourier transform (FT) and diode-array (DA) near-infrared spectra of Formulation I.*
(LVs: number of latent variables, RPD: ratio of standard error of performance to standard deviation, RMSE: root mean square error, R^2: square of Pearson's correlation coefficient)

		Pretreatment	LVs	RMSE	RPD	R^2
DS	calibration	—	9	0.095	13.91	0.9948
	cross-validation			0.261	5.29	0.9642
	calibration	SNV Savitzky-Golay 2nd derivative	3	0.089	14.85	0.9955
	cross-validation			0.125	11.03	0.9918
FT	calibration	—	6	0.125	10.62	0.9911
	cross-validation			0.216	6.39	0.9755
	calibration	SNV gap-segment 2nd derivative	3	0.083	16.00	0.9961
	cross-validation			0.130	10.61	0.9911
DA	calibration	—	2	0.145	9.15	0.9881
	cross-validation			0.171	8.05	0.9846
	calibration	SNV Savitzky-Golay 2nd derivative	2	0.040	32.94	0.9991
	cross-validation			0.045	30.96	0.9990

Table 5. *The PLSR results for the raw spectra and mathematically pretreated dispersive (DS), Fourier transform (FT) and diode-array (DA) near-infrared spectra of Formulation II.*
(LVs: number of latent variables, RPD: ratio of standard error of performance to standard deviation, RMSE: root mean square error, R^2: square of Pearson's correlation coefficient)

		Pretreatment	LVs	RMSE	RPD	R^2
DS	calibration	—	8	0.113	8.81	0.9871
	cross-validation			0.228	4.50	0.9506
	calibration	MSC gap-segment 2nd derivative	4	0.135	7.37	0.9816
	cross-validation			0.193	5.33	0.9648
FT	calibration	—	4	0.312	3.19	0.9018
	cross-validation			0.476	2.16	0.7853
	calibration	MSC	3	0.275	3.62	0.9237
	cross-validation			0.344	2.99	0.8879
DA	calibration	—	4	0.161	6.20	0.9740
	cross-validation			0.185	5.54	0.9674
	calibration	SNV gap-segment 2nd derivative	4	0.101	9.83	0.9897
	cross-validation			0.144	7.13	0.9803

4.2. Sample handling techniques for ATR FT-IR spectroscopic analysis of preparative chromatographic media

To study the possibility of a fast and cost-effective measurement with the ATR FT-IR technique, the measurement of commercially available preparative chromatographic column media was performed both in original suspension form and after drying. The samples in suspension form (hereinafter referred to as the *as is* samples) were measured without any sample preparation. During drying, the possible simplest method was applied without using washing or filtering steps.

The liquid phase of *as is* samples and the moisture content of dried chromatography media samples resulted in characteristic bands of O-H vibrations around 3400 cm^{-1} and 1650 cm^{-1}, and increasing absorption below 900 cm^{-1}. To exclude these O-H regions, the spectral region between 1500 cm^{-1} and 900 cm^{-1} was used for further analyses where the spectra of both *as is* and dried samples showed high similarity. SNV correction was applied to eliminate baseline shifts. PCA was used to investigate the spectral differences between the samples with different support matrices and surface ligands and compare the *as is* and drying measurement methods. The results of PCA confirmed that the spectra provide information about the chemical properties of both the support matrix and the surface ligands. Therefore, they are suitable for implementing the classification of chromatography media samples according to these properties (*Figure 1*).

The identification of 5 chromatography media formulations was performed by SIMCA models, which were generated using simulated spectra to reduce the effects of the small sample size. Both the *as is* and dried sample models provided high sensitivity (> 80%), specificity (> 97%), positive predictive value (PPV > 88%), and negative predictive value (NPV > 97%) results during the sample classification, and there was no significant difference between the *as is* and dried measurement techniques.

The PCA and SIMCA results confirmed that the spectra obtained by the *as is* measurement technique have a similar information content as the spectra of the samples measured after drying, so the time-consuming sample preparation can be omitted. Therefore the measurement can be performed in a few minutes. In addition, the sample required for the *as is* measurement is small (only 20 μl).

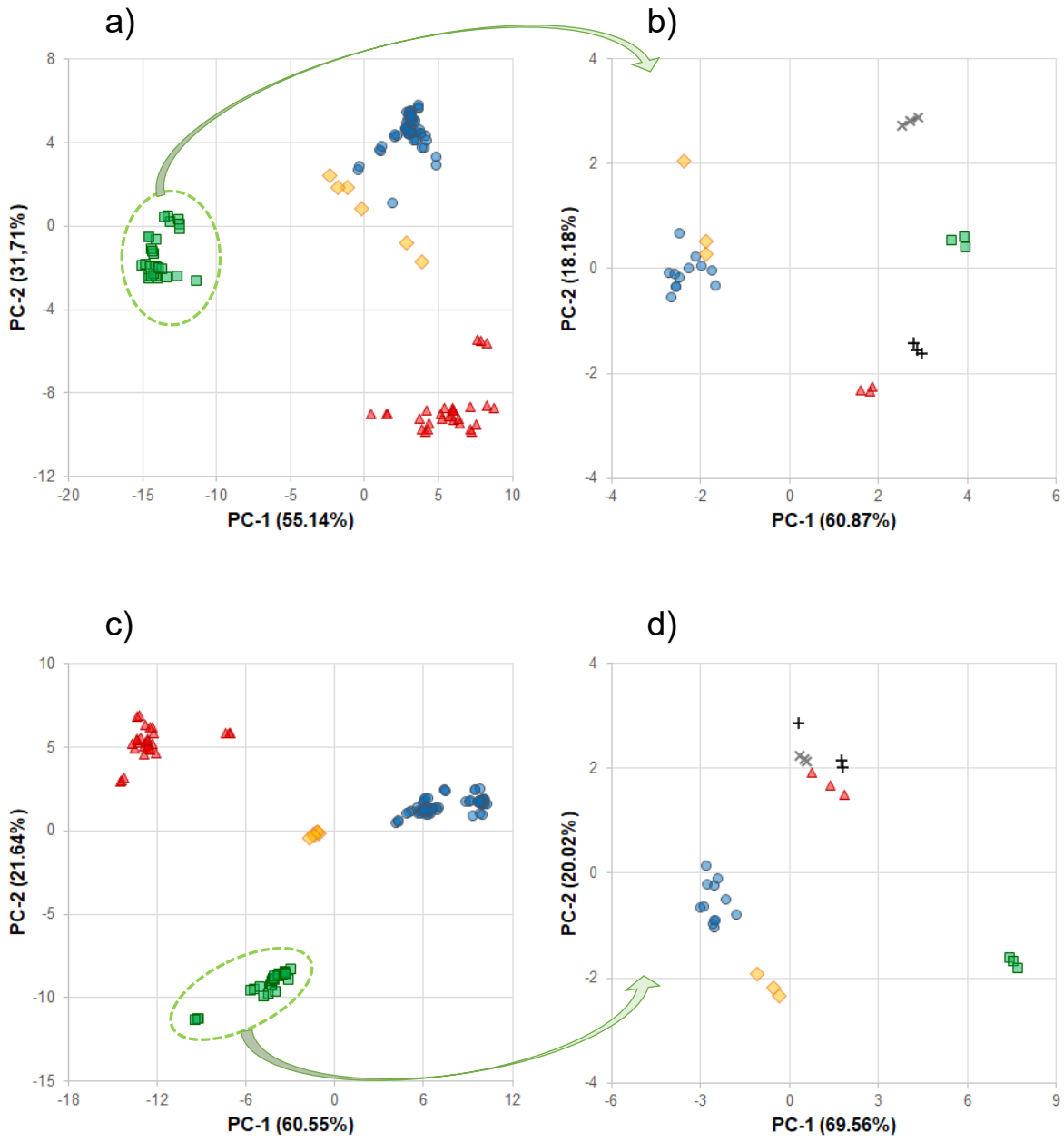

Figure 1.

Left: PCA score plots of ATR FT-IR spectra of chromatography media samples measured in original suspension form (a) and after drying (c). Plots are colored according to support matrix:
●*: agarose,* ■*: metacrylate,* ▲*: poly(styrene-divinylbenzene),* ◆*: glass.*

Right: PCA score plots of ATR FT-IR spectra of methacrylate-based samples measured in original suspension form (b) and after drying (d). Plots are colored according to surface functionality:
●*: sulfoisobutyl,,* ■*: amine,* ▲*: trimethylammoniumethyl,* ◆*: sulfopropyl,* ×*: phenyl,* +*: carboxyl.*

4.3. Comparison of classification methods based on NIR spectra of medium powders

DS and FT-NIR spectra were recorded from medium powders after the heat treatment of samples based on a two-factor, three-level full factorial design. The performed PCA and SIMCA analyses showed that the spectral range between 2200 and 2300 nm indicated the changes caused by the heat treatment. Based on this spectral region of DS spectra, simulated spectra were generated for creating and comparing classification models using PCA-LDA, PLS-DA, and SIMCA methods.

With PCA-LDA models, the identification of the 70 °C samples was perfect in each case. Spectra from the control group mainly were correctly identified with the PCA-LDA models, only one spectrum gave incorrect results and was classified as a 50 °C sample. The PLS-DA models showed poorer results during the classification of the original spectra than PCA-LDA because even the 70 °C samples could not be reliably detected. The SIMCA models gave better results than the PLS-DA models, but the results did not achieve the efficiency of PCA-LDA during the classification of the original spectra. More samples of control class were categorized as members of both the control and the 50 °C classes. Moreover, samples from the 70 °C class could not be reliably assigned to any class in several cases.

Based on the presented procedure, a strategy for model development based on simulated spectra was proposed (Figure 2).

- First, we create several simulated data sets for the model building based on the spectra of an adequately assembled set of samples.
- Then, the obtained models are tested with the original spectra, selecting several models with good performance indicators.
- Finally, the spectra of the newly arrived samples are classified with these models. In the case of consistent results, the classification of the sample can be accepted. If different models give different results, further measurements of the new sample, simulation of spectra, and model development are recommended.

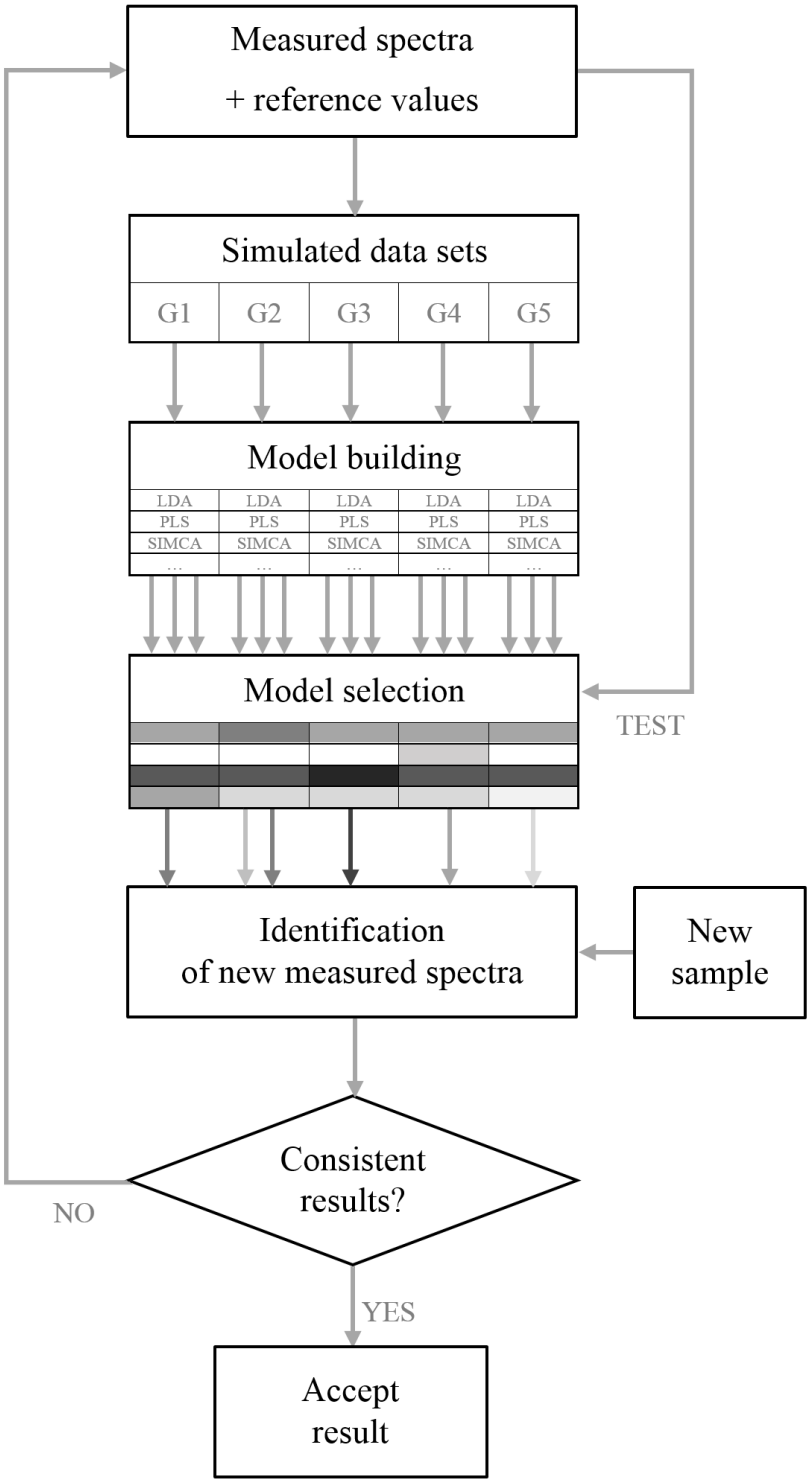

Figure 2. *Flowchart describing the potential use of spectrum simulation based on measured spectra.*

5. Theses

1. I created a strategy to perform model building and model development based on simulated spectra in cases where a small number of available samples would slow down the development of spectroscopic methods (see Figure 2 in the thesis booklet). We create simulated data sets based on the measured spectra to create robust models. Using parallel prediction models facilitates statistical decisions and can be iteratively expanded over longer-term use [I, II, III].

2. I generated chemical fingerprints from the support matrix and surface ligand of the preparative chromatographic media using attenuated total reflection Fourier transform infrared (ATR FT-IR) spectroscopy. Compared to the routine preparative pre-testing of these process aids, the low-cost, high-throughput, and environmentally friendly ATR FT-IR obtains additional information. Furthermore, I established that the spectra between 1500 cm^{-1} and 900 cm^{-1} carry sufficient information to distinguish the chromatography media samples, and I also supported my finding with the results of principal component analysis [I].

3. I developed an ATR FT-IR method that does not require sample preparation to investigate the preparative chromatographic media used for protein purification. I have demonstrated that the drying sample preparation recommended in the literature can be omitted during the samples' correctly performed ATR FT-IR measurement, thus reducing the test time to more than 12 h to 5-10 min [I].

4. I developed calibration models to determine the active pharmaceutical ingredient content of two transdermal gel formulations with different compositions between 1.0 - 5.0% (w/w) and 0.5 - 3.0% (w/w) using three near-infrared (NIR) spectrophotometers with different optical arrangements. The accuracy and robustness of the six independently developed partial least squares regression (PLSR) models were confirmed using simulated spectra [II].

5. I demonstrated that depending on the type of the NIR spectrophotometer (e.g. optical arrangement, measuring range, detector, light source), the accuracy of the calibration developed for the quantitative examination of transdermal gels may differ significantly. Of the devices I tested, the PLSR models based on the spectra of the diode-array NIR

spectrometer gave the least mean square error during cross-validation [RMSECV <0.15% (w / w)], these models are suitable for replacing the time-consuming, expensive, and less environmental-friendly liquid chromatography measurements [II].

6. I examined the medium powder developed for the fermentation of Chinese hamster ovary cells with dispersive and Fourier transform NIR spectrophotometers. I proved that the changes in the heat-sensitive ingredients are best shown in the dispersive NIR spectra and the range of 2200-2300 nm containing the C-O, C=O, C-H, O-H absorption bands of the bioactive components [IV].

7. I developed classification models for the detection of heat-treated media powders using linear discriminant analysis combined with principal component analysis (PCA-LDA), partial least squares discriminant analysis (PLS-DA) and soft independent modeling of class analogy (SIMCA) based on simulated spectra generated in the spectral range between 2200-2300 nm. Based on the correct and incorrect classification ratio (CC% and IC%), the PCA-LDA outperformed PLS-DA and SIMCA during the classification of the heat-treated and control samples (CC% > 92%; IC% < 8%), so it can be used as a fast and environmentally friendly technique to identify improperly stored media powder samples [III].

6. Potential applications

In my PhD work, I presented the results of the development of infrared spectroscopic methods as a fast and non-destructive alternative at certain stages of the pharmaceutical quality control process. My measurements were aimed at the qualitative and quantitative analysis of raw materials, process aids and end products, which are currently classified by expensive and time-consuming preparative methods or separation techniques.

The diode-array NIR measurement technique developed for the quantitative analysis of transdermal gels using PLSR models can complement or even replace the time-consuming liquid chromatography measurements used in everyday practice.

By measuring the preparative chromatographic column packings, I demonstrated that the ATR FT IR could be used to obtain a chemical fingerprint of the chromatography media samples in a few minutes without sample preparation.

The simulation-based model development technique presented with the spectra of medium powders can be applied to other feasibility studies when the number of samples required to optimize multivariate models is not available.

I hope that the results I present will facilitate the work of pharmaceutical quality control laboratories in the longer term by providing fast, cost-effective and environmentally friendly infrared spectroscopic methods and contributing to the development of industrial digitization.

7. Publication list

Publications related to PhD theses in journals with impact factor

I É. Szabó, L. Z. Baranyai, Z. Sütő, A. Salgó, S. Gergely (2020): Attenuated total reflection fourier transform infrared spectroscopy based methods for identification of chromatography media formulations used in downstream processes. *Journal of Pharmaceutical and Biomedical Analysis* **180**: 11060. DOI: 10.1016/j.jpba.2019.113060 (IF_{2020}: 3.77, I: 1, FI: 1)*

II É. Szabó, S. Gergely, T. Spaits, T. Simon, A. Salgó (2019): Near-infrared spectroscopy based methods for quantitative determination of active pharmaceutical ingredient in transdermal gel formulations. *Spectroscopy Letters* **52(10)**: pp. 599-611.
DOI: 10.1080/00387010.2019.1681459 (IF_{2019}: 0.97, I: 2, FI: 2)

III É. Szabó, S. Gergely, A. Salgó (2018): Linear discriminant analysis, partial least squares discriminant analysis, and soft independent modeling of class analogy of experimental and simulated near-infrared spectra of a cultivation medium for mammalian cells. *Journal of Chemometrics* **32(4)**: e3005. DOI: 10.1002/cem.3005 (IF_{2018}: 1.79, I: 4, FI: 2)

IV É. Szabó, L. Párta, D. Zalai, S. Gergely, A. Salgó (2016): Investigation of heat-treated cultivation medium for mammalian cells with near infrared spectroscopy. *Journal of Near Infrared Spectroscopy* **24(4)**: pp. 373-380. DOI: 10.1255/jnirs.1222 (IF_{2016}: 1.07, I: 2, FI: 0)

Other publications in journals with impact factor

V Á. Mári, G. Bordós, S. Gergely, M. Büki, J. Háhn, Z. Palotai, G. Besenyő, É. Szabó, A. Salgó, B. Kriszt, S. Szoboszlay (2021): Validation of microplastic sample preparation method for freshwater samples. *Water Research* **202**: 117409. DOI: 10.1016/j.watres.2021.117409 (IF_{2020}: 11.3)

VI G. Bordós, S. Gergely, J. Háhn, Z. Palotai, É. Szabó, G. Besenyő, A. Salgó, P. Harkai, B. Kriszt, S. Szoboszlay (2021): Validation of pressurized fractionated filtration microplastic sampling in controlled test environment. *Water Research* **189**: 116572. DOI: 10.1016/j.watres.2020.116572 (IF_{2020}: 11.3)

VII E. Kontsek, A. Pesti, M. Björnstedt, T. Üveges, É. Szabó, T. Garay, P. Gordon, S. Gergely, A. Kiss (2020): Mid-infrared imaging is able to characterize and separate cancer cell lines. *Pathology & Oncology Research* **26**: pp. 2401–2407. DOI: 10.1007/s12253-020-00825-z (IF_{2020}: 2.75)

VIII J. Slezsák, É. Szabó, S. Gergely, A. Salgó (2018): Measuring of food industrial raw materials via polyethylene packages by NIR spectrophotometers using different optical arrangements. *Acta Alimentaria* **47(1)**: pp. 104-112. DOI: 10.1556/066.2018.47.1.13 (IF_{2018}: 0.57)

IX Südy Á., Szabó É., Salgó A. (2013): Sztevia – egy természetes eredetű édesítőszer. *Élelmiszer Tudomány Technológia* **67(2)**: pp. 27-31.

* IF: impact factor in the given year, I: citations, FI: independent citations.

Publications in international conference proceedings related to PhD thesis

X É. Szabó, S. Gergely, A. Salgó: Multivariate data analysis of near-infrared spectra of cultivation medium powders for mammalian cells. In: S.B. Engelsen, K.M. Sørensen and F. van den Berg (eds.), Proceedings of the 18th International Conference on Near Infrared Spectroscopy. IM Publications Open, Chichester, 2019. pp. 143-150. DOI: 10.1255/nir2017.143

Other publications in international conference proceedings

XI Slezsák J., Szabó É., Gergely Sz.: Gyógyszeripari alapanyagok polimer csomagolóanyagokon keresztül való mérése különböző optikai elrendezésű NIR spektrofotométerekkel. In: Abonyi J., Klein M., Balogh A. (szerk.), Műszaki Kémiai Napok 2017: Chemical Engineering Conference 2017. Pannon Egyetem, Veszprém, Magyarország, 2017. pp. 91-96.

XII Gergely Sz., Slezsák J., Szabó É., Kondákor A., Salgó A.: Az infravörös spektroszkópia lehetőségei a csomagolóanyagok vizsgálatában. In: Szigeti T.J., Popovics A. (szerk.), Hungalimentaria 2017 konferencia és kiállítás: Terítéken az élelmiszerek és csomagolóanyagaik. Wessling Hungary Kft., Budapest, Magyarország, 2017. pp. 35-36.

Conference abstracts related to PhD thesis

XIII É. Szabó, S. Gergely, A. Salgó: Multivariate data analysis of near-infrared spectra of cultivation media for mammalian cells. Conferentia Chemometrica (September 3-6, 2017; Gyöngyös-Farkasmály, Hungary). Abstracts: P29

XIV Szabó É., Gergely Sz.; Salgó A.: Közeli infravörös spektroszkópiai módszerek fejlesztése gyógyszeripari minőségbiztosítási célokra. Oláh György Doktori Iskola XIV. Konferenciája (2017. február 2.; Budapest). Abstracts: SzÉ

XV É. Szabó, S. Gergely, A. Salgó: Investigation of heat-treated cultivation medium for mammalian cells with near-infrared spectroscopy: chemometrics in the service of spectroscopy. 16th Chemometrics in Analytical Chemistry Conference (June 6-10, 2016; Barcelona, Spain). Book of abstracts: Szabo et al.

XVI Szabó É.: Hőhatásnak kitett emlőssejtes tápoldatporok vizsgálata infravörös spektroszkópiai- és preparatív, lombikos minősítési módszerekkel. XXXII. Országos Tudományos Diákköri Konferencia – Kémiai és Vegyipari Szekció (2015. április 9-11.; Veszprém). Kivonatok: pp. 70-71.