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Forensic Science International 134 (2003) 187–195

Forensic Science International

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Analysis of ecstasy tablets: comparison of reflectance and transmittance near infrared spectroscopy

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Received 10 October 2002; received in revised form 1 April 2003; accepted 1 April 2003

Abstract

Calibration models for the quantitation of commonly used ecstasy substances have been developed using near infrared spectroscopy (NIR) in diffuse reflectance and in transmission mode by applying seized ecstasy tablets for model building and validation. The samples contained amphetamine, *N*-methyl-3,4-methylenedioxy-amphetamine (MDMA) and *N*-ethyl-3,4-methylenedioxy-amphetamine (MDE) in different concentrations. All tablets were analyzed using high performance liquid chromatography (HPLC) with diode array detection as reference method. We evaluated the performance of each NIR measurement method with regard to its ability to predict the content of each tablet with a low root mean square error of prediction (RMSEP). Best calibration models could be generated by using NIR measurement in transmittance mode with wavelength selection and $1/x$-transformation of the raw data. The models build in reflectance mode showed higher RMSEPs using as data pretreatment, wavelength selection, $1/x$-transformation and a second order Savitzky–Golay derivative with five point smoothing was applied to obtain the best models. To estimate the influence of inhomogeneities in the illegal tablets, a calibration of the destroyed, i.e. triturated samples was build and compared to the corresponding data of the whole tablets. The calibrations using these homogenized tablets showed lower RMSEPs. We can conclude that NIR analysis of ecstasy tablets in transmission mode is more suitable than measurement in diffuse reflectance to obtain quantification models for their active ingredients with regard to low errors of prediction. Inhomogeneities in the samples are equalized when measuring the tablets as powdered samples.

Keywords: Forensic science; NIR; MDMA; MDE; Amphetamine; Ecstasy

1. Introduction

An increasing abuse of amphetamine and its methylenedioxylated derivates is being registrated by official criminological authorities [1]. These drugs of abuse presented as tablets on the street are commonly defined as ecstasy (for structures, see Fig. 1). To carry out further steps during investigation of these illegal drugs after their confiscation, a fast and reliable determination of the tablet's ingredients is crucial. Many methods have been developed for their determination. Analysis may be performed by applying immunoassays [2], gas chromatography (GC) [3,4], capillary electrophoresis (CE) [5,6] or liquid chromatography (LC) [7–10]. But all of these methods have to destroy the pieces of evidence, i.e. the tablets to determine the illegal substances. Sondermann and Kovar [10,11] developed a method using near infrared spectroscopy (NIR) to identify and quantify the commonly used substances of abuse being found in ecstasy tablets. This validated method proved to be fast and precise without destroying the samples. So after determining the illegal substances, the pieces of evidence could be presented at court. To build a robust calibration, Sondermann et al. used self manufactured tablets. As these tablets were made with pharmaceutical knowledge by using chemical pure substances, this calibration can only reflect a part of the variety of the tablets existing on the illegal markets. The aim of our study was to develop a method of quantification for the mainly used substances of abuse being found in ecstasy

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0379-0738/03/$ – see front matter © 2003 Published by Elsevier Science Ireland Ltd.
doi:10.1016/S0379-0738(03)00125-7

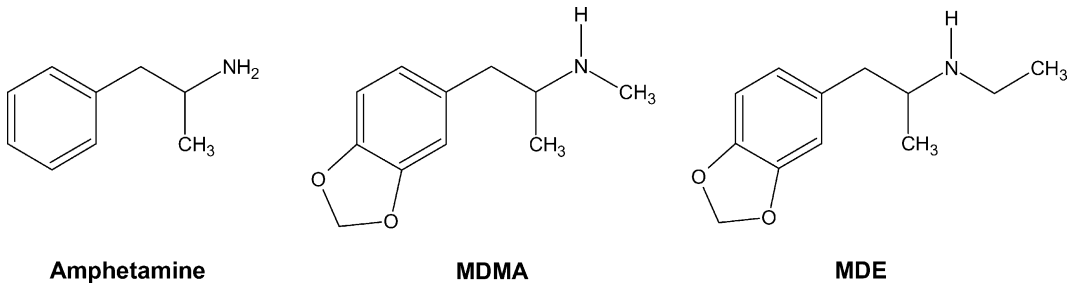

Fig. 1. Structure of analyzed substances.

tablets by means of tablets seized by the police. So an extensive variety of different tablets could be taken into account. All differing in seize, weight and diameter. Further on we wanted to find out, whether NIR measurements in transmission or in reflection mode would give better results, i.e. lower errors of prediction. To evaluate if pulverizing the tablets would influence the analysis, the triturated samples were investigated by NIR measurement in reflectance mode. The results were compared to determine the most suitable method.

2. Materials and methods

2.1. Confiscated samples

Seized ecstasy tablets were obtained from the Bundeskriminalamt (BKA) in Wiesbaden, the Federal Bureau of Criminal Investigation in Germany. The samples were grouped in nine sets, each set differing from the other with regard to their imprinted picture. For detailed information see Table 1.

2.2. Sample preparation

No sample preparation was necessary for NIR measurements of the unbroken tablets, as they were either measured directly on a glass plate (for measurement in reflectance mode) or entirely put in a tablet holder (measurement in transmittance mode). Each tablet was then pulverized in a mortar with a pestle to fine homogeneous powder. Then, the powders were quantitatively poured in identical glass vials (Fisher Scientific, Germany).

2.3. HPLC parameters

The analytical test method for the determination of the composition of each individual tablet was high performance liquid chromatography (HPLC). The HPLC system consisted of a L-7200 LaChrom Autosampler, L-6200A Intelligent Pump and L-7455 Diode Array Detector (Merck Hitachi, Germany). The chromatographic data was recorded and processed by the D-7000 Interface Module and the D-7000 HPLC-System-Manager Version 4.0 from Merck, Germany. Analyses were carried out on a Chromolith SpeedRod RP-18e column (50 mm × 4.6 mm, Merck, Darmstadt, Germany) using as pre-column a LICHROSPHER 100 RP-18e (5 μm, 4 mm × 4 mm). A gradient was employed to elute the compounds. Solvent A was composed of a phosphate solution (20 mM KH_2PO_4) with an addition of 0.1% triethylamine and adjusted to pH 2.28 with phosphoric acid (85%). Solvent B was acetonitrile. The gradient was processed as followed: 0–2 min 94% solvent A (isocratical elution), from 2 to 8 min changing to 87% solvent A (gradient elution), 8–13 min staying isocratical at 87% solvent A. The flow rate during all analyses was kept constant at 1.5 ml min^{-1}. Equilibration time was 7 min. Detection was performed using a variable wavelength program: 210 nm

Table 1
Data of the tablets analyzed (ranges)

Set	Imprinted picture	Weight (mg)	Height (mm)	Diameter (mm)
1	Pitbull	215.28–225.64	3.05–3.30	9.10–9.20
2	Bad boy	240.65–256.49	3.65–3.85	9.10–9.20
3	Sparrow	226.68–241.75	4.05–4.15	8.30–8.40
4	Elephant	273.53–308.78	3.90–4.20	8.60–8.65
5	Butterfly	192.12–242.40	3.25–4.00	8.30
6	“e”	179.33–210.38	3.05–3.50	8.20
7	“X-files”	261.56–292.64	4.30–4.60	9.15–9.25
8	“€”	285.82–305.67	3.50–4.65	9.15–9.40
9	“CK”	246.31–253.25	4.00	8.20–8.25

from 0 to 3.5 min and 285 nm throughout the rest of the HPLC run. The whole analysis was performed using metoclopramide as internal standard. For detailed description of the development, validation of the method and statistical parameters see [12].

2.4. NIRS measurement

The NIR spectra were collected in diffuse reflective mode on a Direct Contact Analyzer (FOSS NIRSystems, Silverspring, MD) and in transmission mode on a InTact Tablet Analyzers (FOSS NIRSystems, Silverspring, MD). The spectra were recorded at 2 nm intervals in the range of 1100–2500 nm for diffuse reflectance and 600–1900 nm in transmittance mode. To reduce noise each spectrum was determined by averaging 32 scans. Both sides of the tablets were analyzed twice this way on two different days. The powders were measured in diffuse reflection twice by shaking the samples between the measurements in order to vary the packaging of the powder in the vials. A highly reflective ceramic standard served as reference in reflection mode. In transmission mode, air was used as standard reference. All spectra were log rationed against the corresponding standard. Spectrometer diagnostics and acquisition of the spectroscopic data were carried utilizing VISION spectral analysis software Version 2.21 (FOSS NIRSystems, Silverspring, MD). All chemometrical calculations were performed using the multivariate analysis software package UNSCRAMBLER Version 7.01 (Camo AS, Norway). All calculations used log (1/reflectance) data [11].

2.5. Spectra pretreatments and chemometrics

During method development raw data and diverse spectra pretreatments were used to calculate the best calibration models. Data treatment was performed using the raw data of the different NIR measurements, Savitzky–Golay derivation with smoothing of the spectra and $1/x$-transformation of the measured values. The $1/x$-transformation reflects the change of the data set from the level of wavelengths to the level of wavenumbers (corresponding to [13]). After reduction of the data sets by wavelength selection to the important regions, partial least squares (PLS) calibrations were used, according to Martens and Naes [14]. The developed models were evaluated by full cross validation (FCV) (leave one out validation) and by validation with an external testset.

2.6. Model data set

The training set of tablets used for calibration was composed of 135 samples, 90 of which contained *N*-methyl-3,4-methylenedioxy-amphetamine (MDMA), 30 *N*-ethyl-3,4-methylenedioxy-amphetamine (MDE) and 15 amphetamine. As every tablet was measured on every side on two different days, the data set was composed of 540 sample spectra. The training set of powder measurements used for comparison with the measurements of the non-triturated tablets was composed of 120 samples, the 90 powdered MDMA tablets and the 30 powdered MDE tablets. As every powder vial was measured twice, the total number of spectra was 240 for this training set.

3. Results

3.1. Proceeding

After measurement of the tablets in transmission and reflectance mode, their actives were determined by a validated HPLC-DAD method [12]. Then, the triturated tablets were measured in reflectance mode to compare the calibration models. Measurement of the powders in transmission mode could not be performed due to the lack of a transmission sample holder for powders. The obtained data of HPLC were correlated to the corresponding sample spectra with the help of the chemometrical software. For all calculations, the content of the constituents was calculated in percent per tablet (w/w) on the basis of the salts of the individual substances. Individual calibration models for each type of NIR measurement were developed. Validation was

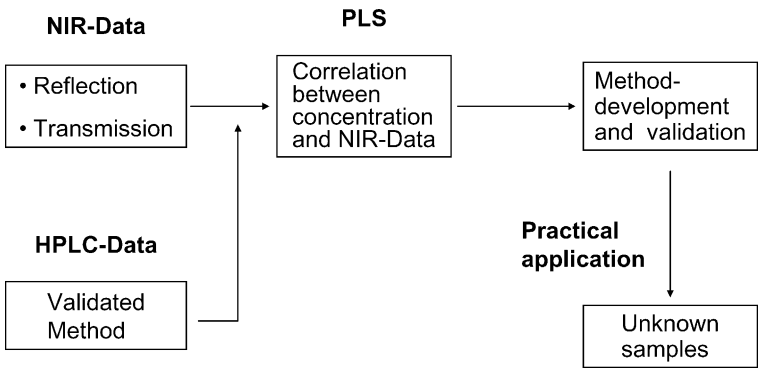

Fig. 2. Proceeding of the calibration.

Table 2
Results of the tablet analysis by reference method (ranges)

Set	Imprinted picture	Substance	Content per tablet (mg)	Mean (mg)	Content per tablet (% (w/w))	Mean (% (w/w))
1	Pitbull	MDE	54.74–60.52	57.65	25.26–27.53	26.20
2	Bad boy	MDE	63.47–85.89	73.20	25.30–34.12	29.31
3	Sparrow	MDMA	70.95–80.55	74.67	29.85–33.59	31.42
4	Elephant	MDMA	54.54–76.63	67.27	19.94–25.40	23.32
5	Butterfly	MDMA	68.36–88.54	75.88	34.29–38.13	36.26
6	"e"	MDMA	64.10–77.64	69.52	34.27–39.30	36.30
7	"X-files"	Amphetamine	19.65–31.79	24.78	7.22–11.68	9.03
8	"€"	MDMA	68.87–81.39	75.73	23.60–27.15	25.76
9	"CK"	MDMA	82.75–94.18	88.85	33.45–37.19	35.65

performed using either full cross validation or validation with an external data set. An overview of the calibration scheme is shown in Fig. 2.

3.2. Reference method

After pulverizing the seized ecstasy samples the amphetamines being in the illicit tablets were determined by liquid chromatography. The analysis of the samples showed that there was only one active per tablet. No mixtures of amphetamine homologues could be found. The tablets containing amphetamine additionally all contained caffeine as additive. The range of the contents of the actives with regard to the different amphetamine groups were 54.54–94.18 mg for MDMA, 54.74–85.89 mg for MDE and 19.65–31.79 mg for amphetamine, respectively. An overview of the results concerning their contents in milligram and percent (w/w) per tablet for each specific sample group can be seen in Table 2.

3.3. Calibration based on diffuse reflection spectra

During method development, different PLS-1 calibrations were performed applying diverse data pretreatments. Exemplarily, this data is shown for the calibration of the constituent MDMA. A PLS-1 calibration with the raw data of the diffuse reflection spectra resulted in a correlation coefficient (R^2) of 0.9448 for the calibration when applying full cross validation. The root mean square error of calibration (RMSEC) was calculated with 1.75% and root mean square error of prediction (RMSEP [14]) with 1.78%, respectively. When restricting the data to the wavelengths of combination bands of the vibrations of CH, CH_2 and CH_3 bonds [15], the greatest differences between the molecules analyzed, and cutting out the wavelengths of the vibration of the OH bonds of water and sugars [15] used as excipients, the final data set consists of the wavelengths set from 1100 to 1400 and 1458 to 1900 nm. The calculation resulted in a R^2 of 0.9741, a RMSEP of 1.21% and a RMSEP of 1.28%. This indicates that restricting the data set to the important variables results in a model which allows to calculate the concentration of the constituent more precisely. The best results for the calibration could be achieved by applying a $1/x$-transformation to the x-data matrix and Savitzky–Golay second derivative with five point smoothing in addition. This could also be confirmed for the calculation of the other constituents. Applying a signal noise variate (SNV) treatment to the x-matrix could not improve the predictive power of the models (data not shown). Model validation was also performed by randomly splitting the data set into calibration and external validation data set (for MDMA: 264 samples as calibration data set and 96 samples as validation data set; MDE: 88 calibration and 32 validation). The statistical data of the calibrations of MDMA, MDE and amphetamine can be seen in Table 3.

3.4. Calibration based on transmission spectra

The procedure for development of the calibration based on transmission spectra was applied analogue to reflectance data.

Table 3
Statistical data of the calibrations for the constituents in NIR reflectance mode

	Number of principal components	Correlation (R^2)	RMSEC[a]	RMSEP[b]
MDMA, testset	5	0.9674	1.3614	1.2817
MDMA, FCV	6	0.9728	1.2368	1.2927
MDE, testset	6	0.9573	0.7500	0.9069
MDE, FCV	6	0.9527	0.7811	1.0369
Amphetamin, FCV	9	0.9782	0.2595	0.8351

[a] Root mean square error of calibration.
[b] Root mean square error of prediction.

Table 4
Statistical data of the calibrations for the constituents in NIR transmittance mode

	Number of principal components	Correlation (R^2)	RMSEC[a]	RMSEP[b]
MDMA, testset	5	0.9848	0.9339	0.7975
MDMA, FCV	5	0.9860	0.8892	0.9103
MDE, testset	2	0.9406	0.8854	0.4882
MDE, FCV	6	0.9701	0.6236	0.6696
Amphetamin, FCV	5	0.9355	0.4420	0.5246

[a] Root mean square error of calibration.
[b] Root mean square error of prediction.

Table 5
Statistical data of the calibration after measurement in NIR reflectance mode of the powdered samples compared to the calibration of the whole tablets

	Number of principal components	Correlation (R^2)	RMSEC[a]	RMSEP[b]
MDMA tablets	6	0.9728	1.2368	1.2927
Powdered MDMA samples	5	0.9891	0.7872	0.8971
MDE tablets	6	0.9527	0.7811	1.0369
Powdered MDE samples	2	0.9708	0.6168	0.6155

[a] Root mean square error of calibration.
[b] Root mean square error of prediction.

PLS-1 calibration with the raw data of the transmission data resulted in a correlation coefficient (R^2) of 0.9820 for the calibration when applying full cross validation. The root mean square error of calibration was calculated with 1.01% and root mean square error of prediction (RMSEP) with 1.07%, respectively. Restriction of the data set to the wavelengths of the second overtones of the vibration bands of CH, CH_2 and CH_3 bonds and the exclusion of the OH vibration bands (water and sugars, see above), also improved the model. The new data set for model building included the wavelengths from 800 to 1350 nm. Calibration with the lowest error of prediction could be calculated after applying $1/x$-transformation to the data matrix. Neither Savitzky–Golay derivation nor SNV treatment could improve the models. For a summary of the statistical data for all constituents calculated with full cross validation or external data set (analogical to reflection mode) (see Table 4).

3.5. Diffuse reflection spectra of the powder

Ecstasy tablets are being produced under non-pharmaceutical conditions, i.e. the ingredients used are of non-pharmaceutical grade and the tablets might have inhomogeneities due to the lack of a non-validated mixing procedure of the active and the excipients. To evaluate if the inhomogeneities of these illegally produced tablets influence the analysis, calibrations were performed by using NIR measurements in reflectance mode of the pulverized tablets and comparing them to the calibrations of the corresponding untriturated tablets. The same data pretreatments were performed as for measurement in reflectance mode (see above). Model building with PLS-1 calculation and FCV was carried out after wavelengths selection (1100–1400 and 1458–1900 nm), $1/x$-transformation and Savitzky–Golay second derivative with five point smoothing. Exemplarily, the calculations of the powders of the MDMA and MDE samples in comparison to their corresponding calibrations as whole tablets are shown in Table 5.

4. Discussion

4.1. Comparison of calibration models and validation

As for calibration models of every constituent in reflection mode, models with the best prediction power, i.e. the lowest error of prediction, were achieved by wavelength selection, $1/x$-transformation and second order Savitzky–Golay derivation with five point smoothing. Removing the vibration bands of water, increased the performance of the models, as water content is a great difference between the samples and thus influences the NIR calibration. The vibration bands in the regions of small wavelengths are amplified using $1/x$-transformation and so contributing more influence to the models. Which is not the case when using the unmodified raw data (see Fig. 3). The slightly better results throughout the validation when using an external testset may be due to the convenient sample selection when randomly choosing them. The calibration for amphetamine was only validated by FCV due to the small data set.

The best models for calibration in transmission mode could be performed by restricting the x-matrix to the important data

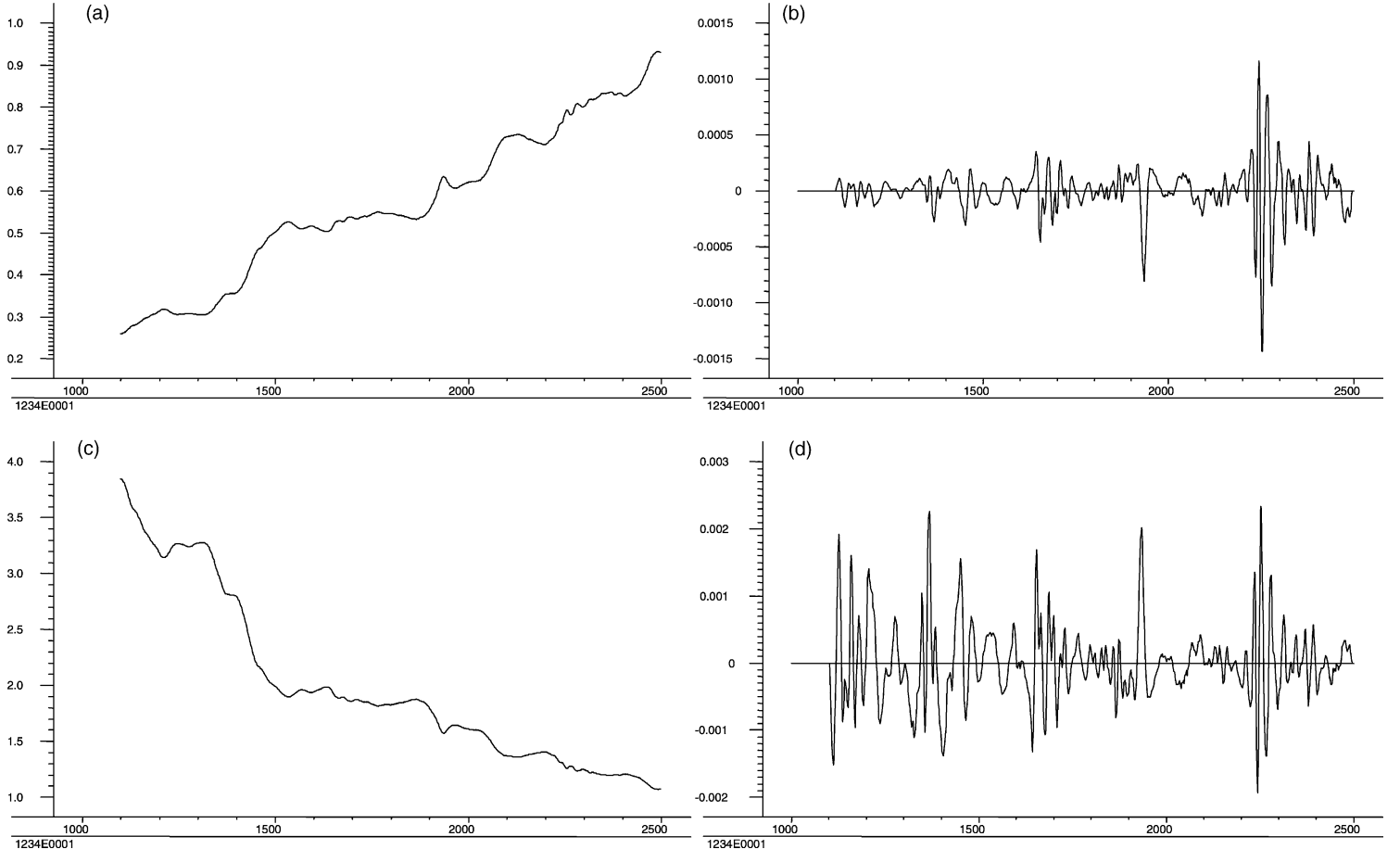

Fig. 3. Spectra (diffuse reflection of one sample (x-axis = wavelength, y-axis = absorption)). (a) Raw data; (b) raw data after Savitzky–Golay derivation (second derivative, five point smoothing); (c) raw data with $1/x$-transformation; (d) raw data after $1/x$-transformation and Savitzky–Golay derivation (second derivative, five point smoothing).

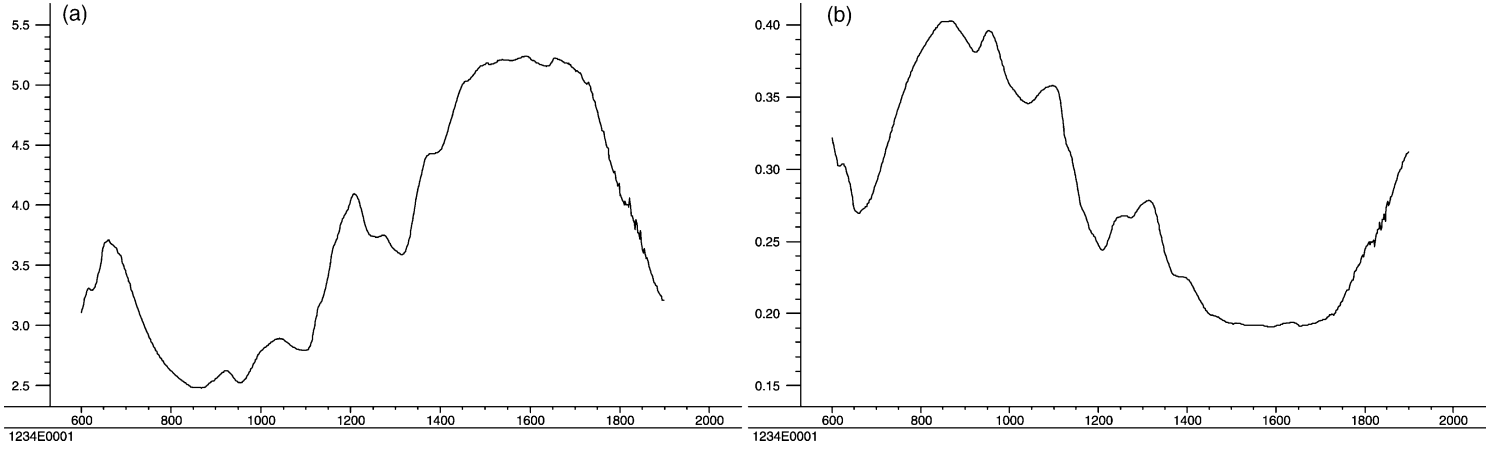

Fig. 4. Spectra (transmission of one sample (x-axis = wavelength, y-axis = absorption)). (a) Raw data transmission; (b) raw data transmission after $1/x$-transformation.

points likewise. The raw data was $1/x$ transformed prior to PLS-1 calculation (see Fig. 4).

4.2. Comparison of data obtained with transmittance and reflectance NIR spectroscopy

When comparing the RMSEP of the calibration models in reflectance mode to those of the measurements in transmission, it can clearly be stated that the calibrations performed using transmission data give lower errors of prediction. As the seized ecstasy tablets have not been produced with pharmaceutical quality, inhomogeneities may occur in the tablets. When data is being collected in diffuse reflection, only a small part of the tablet can be analyzed, as the light of the near infrared instrument can only penetrate a short distance in the tablet before being reflected. So higher errors of prediction are most likely, when comparing the data to HPLC results. If measurement is performed in transmission mode, the light beam penetrates almost the whole tablet prior to detection. Thus, a compensation of possible inhomogeneities exists, as more of the substance is being analyzed, resulting in lower RMSEPs. This conclusion is equivalent to those published by other authors [16–18].

4.3. Comparison of the calibration using tablets or powders

Exemplarily the calibrations of the whole MDMA and MDE tablets and the calibration of the corresponding powders are compared. Calibrations using measurements of the triturated tablets result in lower errors of prediction. So homogenization of the samples is necessary in order to obtain more precise results when analyzing ecstasy tablets.

5. Conclusion

Seized ecstasy tablets, thus not of pharmaceutical quality and all differing in seize and diameter, have been analyzed by near infrared spectroscopy. Quantification models for the mainly used actives have been developed using reference data from a HPLC-DAD method. We could show that NIR measurement in transmission mode of the illicit tablets results in the best models of prediction regarding to measurement in diffuse reflectance mode. Raw data with wavelength selection and $1/x$-transformation have been used to build up calibration models. As for diffuse reflectance data, the best models can be developed using wavelength selection, $1/x$-transformation and second order Savitzky–Golay derivation with five point smoothing. The RMSEP of the analysis can be improved by using powdered tablets for model building with Savitzky–Golay derivation and smoothing, also applying $1/x$-transformation. Calibration and analysis of the whole tablets is negatively influenced due to production depending inhomogeneities in the samples. These differences are equalized when measuring the tablets as powdered samples. Case-sensitive, the most suitable method has to be chosen to quantify the ecstasy tablets; either emphasizing on no sample preparation, so less time consuming analysis, or precision of the method, i.e. powdering the samples. We can conclude that NIR analysis of ecstasy tablets in transmission mode is more suitable than measurement in diffuse reflectance to obtain quantification models for their active ingredients with regard to low errors of prediction.

Acknowledgements

The authors would like to thank the BKA Wiesbaden for providing us with illicit tablets, Foss GmbH (Hamburg, Germany) for donating the spectrometers applied in this work and the Deutsche Forschunggemeinschaft (DFG) for funding this work as part of the Graduiertenkolleg für Analytische Chemie (Tübingen).

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