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The application of NIR spectroscopy with chemometric analysis for monitoring a powder blending process

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Abstract: This paper reports the use of near infrared (NIR) spectroscopy as a process analytical technology (PAT) tool for monitoring the metformin (*N*,*N*--dimethylimidodicarbonimidic diamide) hydrochloride and poly(vinyl pyrrolidone) (PVP) mixing process, which is the first stage in tablet production. Blend homogeneity was tested using the non-invasive NIR spectroscopy method and the partial least squares (PLS) regression model was applied for the analysis of the obtained spectra. Simultaneously, the critical parameter (metformin hydrochloride content) was monitored by a classical analytical technique, the validated HPLC method, commonly used for this purpose. Based on the high sensitivity of the model developed in this study, as well as the established correlation among the results obtained by different methods, it could be concluded that the proposed rapid and non-invasive technique could be an effective tool for the monitoring of one of the critical manufacturing steps in the production solid dosage forms.

Keywords: PAT; NIR spectroscopy; PLS; metformin hydrochloride; blend uniformity analysis.

INTRODUCTION

Process analytical technology (PAT) is defined by the United States Food and Drug Administration (FDA) in the document *Guidance for Industry: PAT – A Framework for Innovative Pharmaceutical Manufacturing and Quality Assurance* as "a system for designing, analyzing, and controlling manufacturing through timely measurements (*i.e.*, during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality".[1]

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Near infrared (NIR) spectroscopy has gained wide acceptance in the agricultural, food and petrochemical industries as a powerful, non-destructive analytical technique. It is an important component of a PAT toolbox, and is the key for enabling Real-Time Release of pharmaceutical tablets. The main advantages of NIR spectroscopy are its rapidity and reliability for on-line and in-line analyses of different products and materials.[2]

Recently, NIR spectroscopy has found increasing use in pharmaceutical analysis for the identification and quality testing of raw materials,[3,4] the monitoring of blending,[5] granulation,[6] moisture content,[5] active substance content,[7–9] roller compaction,[10] drying operations[11] and many other applications.[12]

The preparation of a uniform blend prior to tableting or encapsulation is one of the most important steps in the production of solid dosage forms. Among the various techniques that are applied for this purpose, one-pot processing is a term that includes any technology that combines different unit operations of a pharmaceutical production process into one machine. It is the production of pharmaceutical granules using a wet granulation process in which dry mixing, liquid addition, wet granulation, drying and sizing of the granules are all performed in the same processing vessel.[13] The concept of a single pot processor is to ensure continuous processing. Usually, the determination of homogeneity of a powder blend requires stopping the production process, taking samples and its analysis by some of the most commonly used analytical methods (UV/Vis, HPLC, *etc*.), which are time-consuming. As most of pharmaceutical excipients and active pharmaceutical ingredients (APIs) absorb IR radiation, NIR spectroscopy may be used for drug content determination in order to define the mixing time end-point. In contrast to the conventional methods, NIR spectroscopy in combination with chemometric analysis is an easy, fast and non-destructive analytical technique for quantification of active ingredients in solid samples.

The assay methods for metformin (*N*,*N*-dimethylimidodicarbonimidic diamide) hydrochloride in a powder blend were either HPLC,[14–16] gas chromatography,[17,18] NMR spectrometry,[19] and UV-spectroscopy[20] In contrast to these conventional methods that depend, predominantly, on sample dissolution in a suitable solvent, NIR spectroscopy combined with chemometrical programs have high potential to measure major active ingredients in solid samples.[21–24]

The aim of this study was to develop a reliable NIR spectroscopic method for monitoring the mixing phase, the first critical step within the manufacturing process of immediate release tablets containing metformin hydrochloride as the active substance. The main goal of this work was to introduce this non-destructive method for the routine monitoring of the tablet production process based on the established correlations with the classic analytical technique commonly used for this purpose.

EXPERIMENTAL

Materials

The following substances were used for the preparation of the blend mixture: metformin hydrochloride (Harman Finochem LTD, India) and poly(vinyl pyrrolidone) (PVP, Kollidon® 25, BASF, Germany).

Methods

NIR spectroscopy. The NIR diffuse reflectance spectra were obtained using a Thermo--Nicolet Antaris instrument with an integrating sphere module and an InGaAs detector. The spectra were recorded in the range from 10000 to 4000 cm^{-1} with an 8-cm^{-1} resolution, 16 scans and a one-minute collection time of.

In order to develop a calibration model for the uniformity of blend prediction, a series of calibration samples was prepared (Table I). Each mixture was measured three times and 48 calibration spectra were recorded. NIR spectra of pure metformin hydrochloride and PVP were also measured.

TABLE I. The composition of mixtures used for the development of a calibration model

Metformin hydrochloride content, mass %	PVP content, mass %
70.00	30.00
75.00	25.00
85.00	15.00
87.00	13.00
88.00	12.00
89.00	11.00
90.00	10.00
91.00	9.00
92.00	8.00
93.00	7.00
94.00	6.00
95.00	5.00
96.00	4.00
97.00	3.00
98.00	2.00
99.00	1.00
100.00	0.00

The effectiveness of the calibration model was evaluated by three independent validation blends (Table II).

TABLE II. The composition of the mixtures used for validation

Sample no.	Metformin hydrochloride content, mass %	PVP content, mass %
1	85.00	15.00
2	90.00	10.00
3	95.00	5.00

The reference (HPLC) method. The content of metformin hydrochloride in the samples was determined by a validated HPLC method, using a liquid chromatograph HP 1100 with a

UV/Vis detector (Agilent 1100 HPLC, USA). Separation was achieved on the Kinetex column (100 mm×4.6 mm, 2.6 μm). The following parameters were used for the analysis: injection volume 20 μl, flow rate 1.5 ml min^{-1}, detection wavelength 200 nm, with a mobile phase containing 0.09 % (*w*/*V*) sodium hexanesulfonate, 5 vol. % acetonitrile and 95 vol. % dilute phosphoric acid (0.1 mass %). HPLC-grade water was used as the solvent. The precision and accuracy of the method were determined. The relative standard deviation (*RSD*) of the results for the six simultaneously prepared samples was 0.23 %, the mean value for the recovery of nine prepared samples was 99.79 % and standard deviation (*SD*) was 1.73 %.

Data analysis

Quantitative calibration models were built with partial least squares (PLS) regression using the least squares algorithm. The goal of PLS regression is to establish a linear relationship between the two matrices, spectral data (*X*) and reference values (*Y*). Both *X* and *Y* were modeled in order to determine the variables in the *X* matrix that would best describe the *Y* matrix.[25] The objectives were to model the *X*- and *Y*-matrix first, and then to predict *Y* from *X* according to the equations:

$$X = 1\overline{x}' + TP' + E \quad (1)$$

$$Y = 1\overline{y}' + UC' + F = 1\overline{y}' + TC' + G \quad (2)$$

where $1\overline{x}'$ and $1\overline{y}'$ represent the variable averages and originate from the preprocessing step. The information related to the observations was assumed in the scores-matrices *T* and *U*. The information related to the variables is stored in the *X*-loading matrix *P*′ and the *Y*-loadings matrix *C*′. The variation in the data was neglected in the modeling from the *E* and *F* residual matrices.

The PLS regression method was applied by using the TQ Analyst software package (Thermo Nicolet, USA). The quality of the models was assessed in terms of the root mean square error of the calibration (Eq. (3), *RMSEC*):

$$RMSEC = \sqrt{\sum_{i=1}^{N} \frac{\left(\hat{Y}_i - Y_{i,iz}\right)^2}{N}} \quad (3)$$

where $Y_{i,iz}$ is the measured parameter, $\hat{Y}_i$ is the predicted parameter and N is the number of samples for the data set under consideration.

During the calibration step, full cross validation (leave-one-out) was applied to the calibration data set and the root mean square error of the cross validation (*RMSECV*) was obtained for the calibration model (Eq. (4)):

$$RMSECV = \sqrt{\sum_{i=1}^{N} \frac{\left(\hat{Y}_{i,\mathrm{val}} - Y_{\mathrm{val}}\right)^2}{N}} \quad (4)$$

In order to determine the number of principal components, the *PRESS* function was used:

$$PRESS = \sum_{i=1}^{N} \left(\hat{Y}_i - Y_{i,\mathrm{iz}}\right)^2 \quad (5)$$

Root mean square error of prediction (*RMSEP*) can be used for an estimation of the prediction accuracy of the statistical model and can predict *Y* for a new *X*:

$$RMSEP = \sqrt{\sum_{i=1}^{N} \frac{\left(\hat{Y}_{i,\mathrm{val}} - Y_{\mathrm{val}}\right)^2}{N}} \quad (6)$$

where $Y_{i,\mathrm{iz}}$ is the measured parameter, $\hat{Y}_i$ is the predicted parameter, and N is the number of samples for the validation data set.

This parameter defines the contribution of each new introduced principal component to the definition of the dimensions of the statistical model.

Preparation of the blend mixture in production

The blend mixture was prepared by the initial feeding and mixing of metformin hydrochloride and PVP (in the mass ratio 90:10) in a vacuum processor (Roto Cube 600, IMA, Italy) at a mixer speed of 100 rpm and a chopper speed of 700 rpm. The samples were taken from the top, middle and bottom (6×2 g) of the mixer after 5, 10 and 15 min of mixing in order to determine the endpoint when the blend homogeneity was achieved.

RESULTS AND DISCUSSION

Representative NIR spectra of pure metformin hydrochloride, PVP and their blends are shown in Fig. 1.

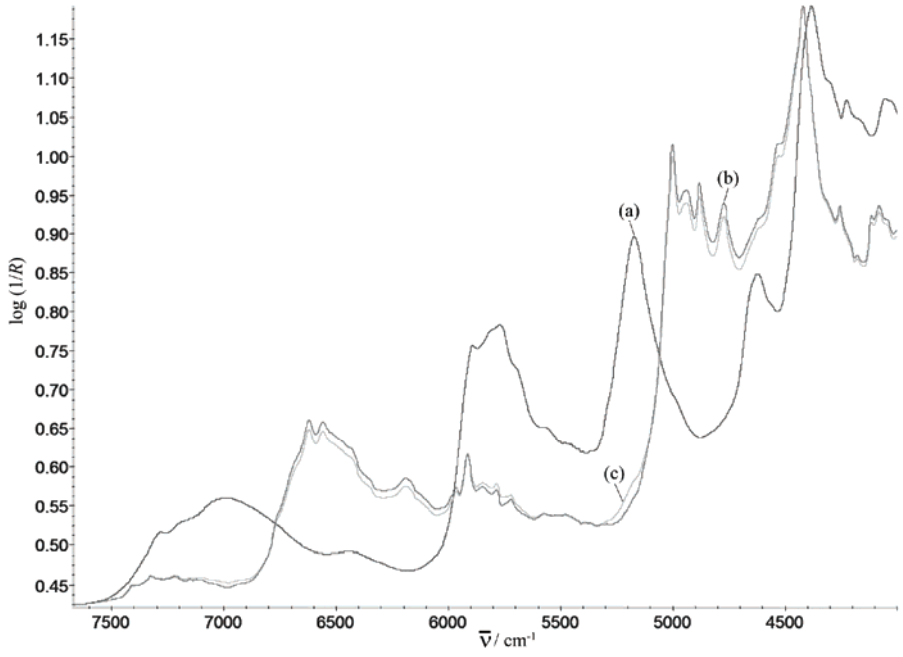

Fig. 1. NIR spectra of: a) PVP, b) metformin hydrochloride and c) mixture of metformin hydrochloride and PVP (mass ratio 90:10).

The NIR spectra of the investigated powder blends indicated that the absorption bands the amino and imido groups of metformin hydrochloride, with peak maxima around 4761, 5924, 6570 and 9600 cm^{-1} (overtones), were associated

with C–H, O–H and C–O combination bands and overtones of PVP, with peak maxima at around 5880 and 4545 cm^{-1}, which are in accordance with the results of Habib and Kamel[26] and Rantanen *et al.*[5]

The spectral range and the number of PLS factors are the two most crucial parameters in the PLS regression process.[27,28] Based on the absorption features observed in the NIR spectra, the two spectral ranges chosen to establish the calibration model were: 5980–5650 cm^{-1} and 5200–4935 cm^{-1}.

The peak maxima in the first region are related to metformin hydrochloride imido groups. The absorbance peak of PVP that appears in the second region enables the creation of the characteristic model for determining the amount of the polymer present in the mixture. The spectra of seventeen calibration samples containing different ratios of the studied components are shown in Fig. 2. Based on the obtained results, it could be seen that the peaks were shifted due to the variations in the composition of the calibration mixture.

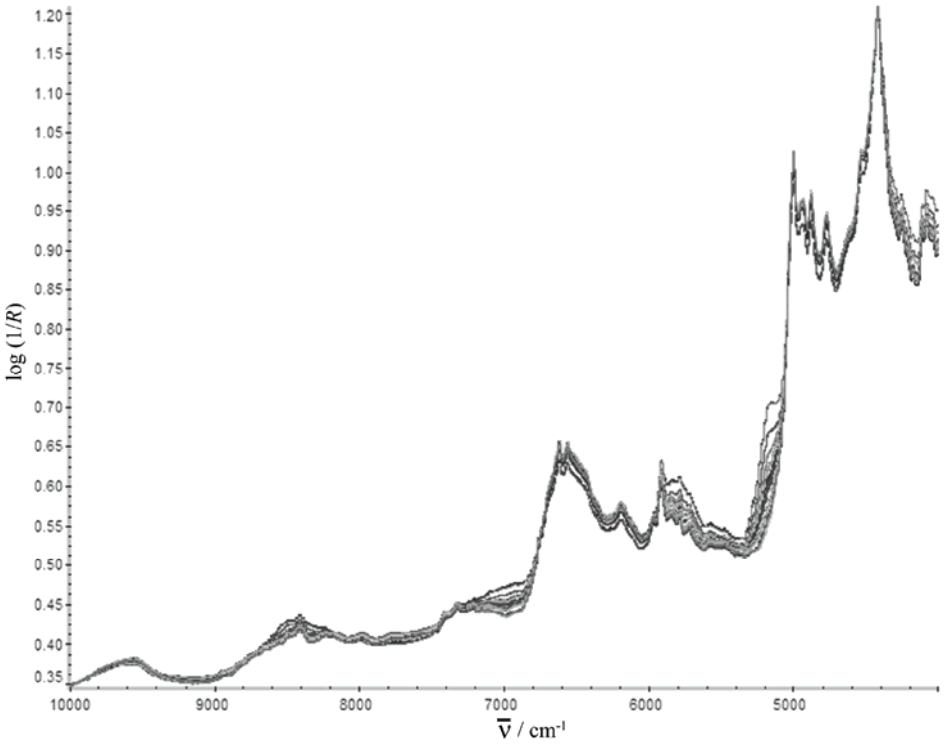

Fig. 2. NIR spectra of the calibration samples.

The calibration and cross-validation regression parameters and the numbers of the principal components in the PLS method, without data pre-treatment, are given in Table III.

TABLE III. PLS calibration models used for the determination of blend uniformity; MTH = = metformin hydrochloride

Parameter	Calibration data set
Number of samples	54
Number of mixtures	16
MTH content in the validation blends (minimal), mass %	69.54
MTH content in the validation blends (maximal), mass %	99.89
Model type	Full spectrum PLS regression
Spectral range, cm^{-1}	5980–5650 and 5200–4935
Number of latent variables	4
Coefficient of correlation	0.9981
RMSEC	0.4810
Coefficient of correlation for cross-validation	0.9956
RMSECV	0.7370

The coefficient of correlation was higher than 0.995, indicating that the established model, with four PLS components, was linear. The lower coefficient of correlation for cross-validation could be attributed to the estimated limit values (mixture of 30 and 70 mass % of PVP and metformin hydrochloride, respectively). The value of this mixture was estimated from the model that was formed over the other sample calibration spectra. In this case, the probability that the linearity of the model was lower is increased, resulting in the consequential increase of the difference between the estimated and actual values, which ultimately results in a slightly lower correlation coefficient.

The results predicted by the NIR method and then checked by the HPLC method for the validation blends are given in Table IV.

TABLE IV. Accuracy and precision of the developed model; number of samples: 6

Parameter	Validation mixture					
	1		2		3	
	Predicted	Measured	Predicted	Measured	Predicted	Measured
Metformin	86.43	84.98	90.05	90.05	95.55	94.97
hydrochloride	86.21	85.12	89.76	89.76	95.23	95.43
content, mass %	85.21	84.96	89.64	89.64	96.02	95.03
	84.22	84.98	90.75	90.75	94.79	94.91
	84.12	85.10	90.53	90.53	94.61	95.28
	84.39	84.94	89.89	89.89	95.11	95.36
Average value, %	85.10	85.01	90.10	90.10	95.22	95.16
SD	1.02	0.08	0.44	0.44	0.51	0.22
RSD	1.20	0.09	0.49	0.49	0.54	0.23
RMSEP	0.930		0.698		0.560	

For the validation mixtures, the calculated recovery values were within the range from 97 to 103 %, *i.e.*, the value was 100.15 % for all the tested samples. The *RSD* and *RMSEP* values of the calibration model were 2 and 1 % lower,

respectively (Table IV). A paired *t*-test statistical comparison at the 95 % confidence level indicated no differences between the results obtained with the two methods. The accuracy and precision of the calibration model were proven based on the obtained results.

The estimated calibration NIR model and HPLC method were used to measure the amount of metformin hydrochloride in the mixture produced in the vacuum processor (production batch). Comparative data obtained by NIR and HPLC analysis are given in Table V.

TABLE V. Comparative results obtained by NIR and HPLC

Mixing time, min	Sampling points in the vacuum processor	Content of metformin hydrochloride in the powder blend mixture, mass %		Difference between the two methods, %
		NIR	HPLC	
5	Top	102.14	99.42	2.72
	Middle	102.19	100.97	1.22
	Bottom	100.27	99.99	0.28
10	Top	101.50	102.13	–0.63
	Middle	101.01	101.93	–0.92
	Bottom	99.31	99.34	–0.03
15	Top	101.01	100.37	0.64
	Middle	100.17	100.38	–0.21
	Bottom	100.56	100.82	–0.27

Based on the obtained data, it could be seen that a homogenous mixture, with a drug content within the range from 95 to 105 % of the theoretical value, was obtained after five minutes of mixing. The difference between the two tested methods for the first set of samples was slightly higher than those for the other two (the samples taken after 10 and 15 min of mixing). This could be attributed to higher sensitivity of the NIR method due to the amount of sample that was exposed to the radiation during spectra collection, which was tens of times higher compared to the amount of sample that was dissolved for the HPLC analysis (*ca*. 30 mg). After the second and the third sampling, the differences between the two methods were lower, which is further confirmation that the calibration model created for a metformin hydrochloride concentration range between 70 and 100 mass % will give reliable results in the analysis of metformin hydrochloride – PVP mixtures.

With regard to defining the final time point of mixing, it could be concluded that homogeneity was achieved after five minutes, which was expected since blending was conducted in a vacuum processor at high mixer and chopper rotation speeds, which enabled homogeneous distributions of the active ingredient to be obtained.

CONCLUSIONS

An NIR spectroscopic method with chemometric analysis was created using the PLS regression model in order to determine the homogeneity of powder mixtures. The calculated results agreed well with those obtained by the HPLC reference analytical method. As a rapid and non-invasive technique, the NIR method reduces sampling errors and provides the possibility of end-point determination, leading to a potentially significant improvement over the conventional analytical methods. Additional work on the implementation of the NIR method in the other phases of tablet production of metformin hydrochloride (granulation, compression) should be realized in order to assure its application for monitoring the entire manufacturing process.

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И З В О Д

ПРИМЕНА NIR СПЕКТРОСКОПИЈЕ ЗА ПРАЋЕЊЕ ПРОЦЕСА МЕШАЊА ПРАШКОВА

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У раду је приказана примена NIR спектроскопије као средства за праћење процеса мешања метформин-хидрохлорида и поливинилпиролидона (PVP) који представља прву фазу у производњи таблета. Хомогеност мешавине тестирана је применом неинвазивне NIR спектроскопије, а за анализу добијених резултата коришћен је регресиони модел најмањих квадрата (PLS). Истовремено је критичан параметар (садржај метформин-хидрохлорида) праћен класичном аналитичком техником која се уобичајено користи у ове сврхе. На основу високе селективности модела развијеног у овој студији, као и успостављеној корелацији између резултата добијених различитим методама, може се закључити да предложена брза и неинвазивна техника може бити ефикасан алат за праћење једне од најкритичнијих производних фаза у изради чврстих дозираних облика.

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REFERENCES

1. FDA, *PAT Guidance for Industry – A Framework for Innovative Pharmaceutical Development, Manufacturing and Quality Assurance*, Rockville, MD, 2004
2. J. Workman, L. Weyer, *Practical Guide to Interpretive Near-Infrared Spectroscopy*, CRS Press, Taylor & Francis Group, Boca Raton, FL, 2008, p. 108
3. G. Reich, *Adv. Drug Deliv. Rev.* **57** (2005) 1109
4. N. K. Shah, P. J. Gemperline, *Anal. Chem.* **62** (1990) 465
5. J. Rantanen, O. Antikainen, J.-P. Mannemiaa, J. Yliiuusi, *Pharm. Dev. Technol*. **5** (2000) 209

6. J. Rantanen, E. Räsänen, O. Antikainen, J. P. Mannermaa, J. Yliruusi, *Chemom. Intell. Lab. Syst*. **56** (2001) 51
7. I. Tomuta, R. Iovanov, A. L. Vonica, S. E. Leucuta, *Sci. Pharm*. **79** (2011) 885
8. P. Chalusa, Y. Roggo, S. Walters, M. Ulmschneider, *Talanta* **66** (2005) 1294
9. S. S. Sekulić, J. Wakeman, P. Doherty, P. A. Hailey, *J. Pharm. Biomed. Anal*. **17** (1998) 1285
10. V. J. Bijlani, M. Delado-Lopez, C. M. Adeyeye, J. K. Drennen, *NIR News* **13** (2002) 8
11. K. R. Morris, J. G. Stowell, S. R. Byra, A. W. Placette, T. D. Davis, G. E. Peck, *Drug Dev. Ind. Pharm.* **26** (2000) 985
12. E. W. Ciurczak, K. James, I. Drennen, *Pharmaceutical and Medical Applications of Near-Infrared Spectroscopy*, Marcel Dekker, New York, 2002, p. 38
13. G. Van Vaerenbergh, *Pharm. Technol. Eur*. **23** (2011) 7
14. M. Kar, P. K. Choudhury, *Indian J. Pharm. Sci.* **71** (2009) 318
15. V. Porta, S. G. Schramm, E. K. Kano, E. E. Koono, Y. P. Armando, K. Fukuda, C. H. dos Reis Serra, *J. Pharm. Biomed. Anal.* **46** (2008) 143
16. R. Huupponen, P. Ojala-Karlsson, J. Rouru, M. Koulu, *J. Chromatogr*. **583** (1992) 270
17. R. Q. Gabr, R. S. Padwal, D. R. Brocks, *J. Pharm. Pharmaceut. Sci.* **13** (2010) 486
18. R. T. Sane, V. J. Banavalikar, V. R. Bhate, V. G. Nayak, *Indian Drugs* **26** (1989) 647
19. S. Z. El-Khateeb, H. N. Assaad, M. G. El-Bardicy, A. S. Ahmad, *Anal. Chim. Acta* **208** (1988) 321
20. M. G. El-Bardicy, S. Z. El-Khateeb, A. K. S. Ahmad, H. N. Assaad, *Spectrosc. Lett*. **22** (1989) 1173
21. C. Ufret, K. Morris, *Drug Dev. Ind. Pharm*. **27** (2001) 719
22. M. Otsuka, F. Kato, Y. Matsuda, *Analyst* **126** (2001) 1578
23. N. Smola, U. Urleb, *Anal. Chim. Acta* **410** (2000) 203
24. K. M. Morisseau, C. T. Rhodes, *Drug Dev. Ind. Pharm*. **21** (1995) 1071
25. M. J. Adams, *Chemometrics in Analytical Spectroscopy*, Royal Society of Chemistry, Cambridge, 1995, p. 30
26. I. Habib, M. S. Kamel, *Talanta* **60** (2003) 185
27. G. X. Zhou, P. A. Hines, K. C. White, M. W. Borer, *Anal. Chem*. **70** (1998) 390
28. K. H. Beebe, B. R. Kowalski, *Anal. Chem*. **59** (1987) 1007A.