AAPS PharmSciTech **2003; 4 (2) Article 19 (http://www.pharmscitech.org).**

Comparative Determination of Polymorphs of Indomethacin in Powders and Tablets by Chemometrical Near-Infrared Spectroscopy and X-ray Powder Diffractometry

Submitted: November 27, 2003; Accepted: March 19, 2003

Makoto Otsuka[1], Fumie Kato[1], Yoshihisa Matsuda[1], and Yukihiro Ozaki[2]

[1]Department of Pharmaceutical Technology, Kobe Pharmaceutical University, Higashi-Nada, Kobe 658-8558, Japan
[2]Department of Chemistry, School of Science, Kawansei-Gauin University, Sanda, 669-1337, Japan

ABSTRACT

The purpose of this research was to develop a rapid chemometrical method based on near-infrared (NIR) spectroscopy to determine indomethacin (IMC) polymorphic content in mixed pharmaceutical powder and tablets. Mixed powder samples with known polymorphic contents of forms α and γ were obtained from physical mixing of 50% of IMC standard polymorphic sample and 50% of excipient mixed powder sample consisting of lactose, corn starch, and hydroxypropylcellulose. The tablets were obtained by compressing the mixed powder at 245 MPa. X-ray powder diffraction profiles and NIR spectra were recorded for 6 kinds of standard materials with various polymorphic contents. The principal component regression analysis was performed based on normalized NIR spectra sets of mixed powder standard samples and tablets. The relationships between the actual and predicted polymorphic contents of form g in the mixed powder measured using x-ray powder diffraction and NIR spectroscopy show a straight line with a slope of 0.960 and 0.995, and correlation coefficient constants of 0.970 and 0.993, respectively. The predicted content values of unknown samples by x-ray powder diffraction and NIR spectroscopy were reproducible and in close agreement, but those by NIR spectroscopy had smaller SDs than those by x-ray powder diffraction. The results suggest that NIR spectroscopy provides a more accurate quantitative analysis of polymorphic content in pharmaceutical mixed powder and tablets than does conventional x-ray powder diffractometry.

Corresponding Author: Makoto Otsuka, Department of Pharmaceutical Technology, Kobe Pharmaceutical University, Higashi-Nada, Kobe 658-8558, Japan. Phone: +81 78-441-7531; Fax: +81 78-441-7532; Email: m-otsuka@kobepharma-u.ac.jp.

KEYWORDS: near-infrared spectroscopy, chemometrics, polymorph, indomethacin, x-ray powder diffractometry

INTRODUCTION

Analytical methods for polymorphism[1-3] in pharmaceutical bulk powders include x-ray powder diffraction,[4] differential scanning calorimetry (DSC),[5] thermogravimetric analysis, microcalorimetry,[6] infrared spectroscopy,[7] Raman spectroscopy,[8] and dissolution kinetics.[9] However, these methods are time-consuming and make it costly to maintain high-quality preparations of samples and/or their measurements. In contrast, near-infrared (NIR) spectroscopy is simple because of its method of nondestructive sample preparation. Consequently, NIR spectroscopy is fast becoming an important technique for pharmaceutical analysis. In addition, chemometrics provides an ideal means of extracting quantitative information from all chemical analytical data[10,11] of multicomponent samples. Calibration methods such as multiple linear regression (MLR), principal component analysis/principal component regression (PCA/PCR), and partial least squares regression are commonly used for quantitative NIR spectroscopy.[12-20] In our previous studies,[12,21] quantitative NIR spectroscopy was applied to evaluate the quality of bulk powder of pharmaceutical products. The degree of crystallinity and polymorphic content of indomethacin (IMC) bulk powder were evaluated by using MLR and PCR. Those valued by NIR spectroscopy were consistent with those obtained by the conventional x-ray powder diffraction, and the accuracy of NIR spectroscopy was more than 50% higher than that of the x-ray method. These results suggested that the quantitative method based on NIR was more accurate and reproducible than x-ray powder diffraction and that handling was easier with NIR than with the conventional methods. On the other hand, Blanco and Villar[22] and Patel et al[23] reported that the polymorphic content in the product con-

sists of drug and excipients, because practical pharmaceutical preparations consist of the bulk drug powder and various kinds of additive powders. In their studies, a powder form sample was applied for the assay, but a tablet form was not. Therefore, the purpose of this study was the systematic quantitative determination of IMC polymorphs in final pharmaceutical preparations, both of mixed powder and of tablet form samples by PCR based on NIR spectroscopy. NIR spectroscopy's accuracy and experimental advantages were compared with those of conventional x-ray powder diffraction.

MATERIALS AND METHODS

Materials

The bulk powder of IMC was obtained from Yashiro Co (Tokyo, Japan). Form a of IMC was prepared by using the following method: 10 g of IMC bulk powder was dissolved in 10 mL of ethanol at 80°C. The undissolved drug was filtered off. Then 20 mL of distilled water at room temperature was added to the IMC-saturated ethanol solution at 80°C. The precipitated crystals were removed by filtration using a glass funnel and then dried under a vacuum at room temperature. Form γ of IMC was prepared by recrystallization from ethyl ether at room temperature.[5] Both sample powders were sieved using 52- and 125-μm screens in a Rowtap shaker (Tanaka Tech Co, Osaka, Japan). Crystalline α-lactose monohydrate (Pharmatose 200M, DeMelkindustrie Veghel Co, Veghel, The Netherlands) and cornstarch (Matsuya Chem Co, Tokyo, Japan) were used as a diluent and a disintegrator, respectively. Hydroxypropylcellulose (HPC) (HPC-LH31; Nihon Soda Co, Tokyo, Japan) was used as a binder. All other chemicals were of analytical grade.

Standard Sample Preparation

The excipient mixed powder was obtained by mixing lactose (DCL 21) 7 g, cornstarch 30 g, and HPC (LH 31) 5 g in a mortar using a pestle. The mixed powders were put into a 200-mL plastic bag, the bag was expanded by air, and then the bag was closed using a rubber band. The bag was placed in the chamber of a V-type mixer (Tokujyu Ind Co, Model V-1, capacity: 2 L, mixing speed: 28 rpm) and mixed for 1 hour. Known quantities of standard IMC mixtures (total amount was 10 g) were obtained by physical mixing of form a and form γ IMC powders at various ratios (0, 20, 40, 60, 80, and 100 wt/wt% form γ content) in a mortar using a pestle. The standard IMC mixtures were mixed in a V-type mixer for 1 hour as described above. Known polymorphic content standard IMC/excipient mixtures (SIEM) were obtained from the careful physical mixing of 50% of the SIEM and 50% of the excipient mixed sample powder in a V-type mixer for 1 hour as described above. Uniformity of the mixing method was tested by measuring the drug concentration of the IMC γ form and excipient mixed powder as follows: After IMC γ form (5 g) and excipient mixed powder (5 g) were mixed using the above mixing method for 10, 20, 30, 60, and 90 minutes, 6 sample powders corrected randomly, and measured individually IMC concentration by UV/visible spectrometer (160A, Shimadzu Co, Kyoto, Japan). The coefficient of variation of the samples reduced with an increase in mixing time, and the values were almost constant at 5% after more than 60 minutes of mixing. Therefore, subsequently, all the samples were mixed for 60 minutes by a V-type mixer.

Tableting Compression Process

A compression/tension tester (Autograph, model IS-5000, Shimadzu Co) was used at 25 ± 1°C. The tablet sample (SIEMT) was obtained to compression 300 mg of SIEM by 8-mm diameter punch with a flat surface in a die at 245 MPa (maximum upper punch pressure, compression speed of 15 mm/min).

X-ray Powder Diffraction Analysis

The x-ray powder diffraction profiles were measured using the following method. The SIEMT was carefully deaggregated in an agate mortar using a pestle, to obtain the powder form of a ground tablet. The x-ray powder diffraction profiles were obtained using an x-ray diffractometer (XD-3A, Shimadzu Co, Kyoto Japan). The measurement conditions included (1) scan mode—step scan, (2) target—Cu, (3) filter—Ni, (4) voltage—20 kV, (5) current—20 mA, (6) receiving slit—0.1 mm, (7) time constant—1 second, and (8) scan width—0.1 degree/step. The silicon powder was measured before and after measuring the x-ray powder diffraction profile of the sample, as an external standard for correction of direct beam intensity. About 80 mg of each sample powder was carefully loaded into a glass holder, and the sample surface was flattened softly without particle orientation by using a spatula and a glass plate. After the x-ray powder diffraction profiles of samples were measured under the above conditions, the intensity values were normalized against the intensity of silicon powder ($2\theta = 28.8°$), which was the external standard. The calibration curves for quantification of crystal content were based on the total relative intensity of the highest 4 independent dif-

fraction peaks, 2θ = 11.6, 19.6, 21.8, and 26.6°, of the form γ crystal. All data were reported as the average of 5 runs.

Thermal Analysis

DSC was performed with a Type 3100 instrument (Mac Science Co, Tokyo Japan). The operating conditions in a open-pan system were as follows: (1) sample weight—5 mg, (2) heating rate—10°C min^{-1}, and (3) N_2 gas flow rate—30 mL min^{-1}.

NIR Spectroscopy

NIR spectra were taken using a Fourier-transformed NIR spectrometer (InfraProver, BRAN+LUEBBE Co, Norderstedt, Germany). Briefly, a fiber-optic probe was inserted into the sample powder (2 g) in a 20-mL glass bottle. The tablet samples were put on the probe and covered with aluminum foil to prevent stray light from getting in. Their NIR spectra were measured. The top surface of the fiber-optic probe had a 12-degree cut angle to prevent reflecting light. The NIR spectra consisted of 459 data points between 1000 and 2222 nm, and 5 scans per sample were recorded. A ceramic (Coor's Standard) reference scan was taken for each set of samples. NIR spectra of 6 kinds of SIEM and SIEMT were recorded 5 times with the NIR spectrometer. A total of 30 spectra, consisting of 24 spectra for the calibration set and 6 spectra for the prediction of calibration, were analyzed by a PCR program associated with the SESAMI software (BRAN+LUEBBE Co).

Quantitative Analysis of Unknown Samples

Unknown polymorphic content IMC samples (UIM) were obtained by a metastable a form transformation to γ form in ethanol reported earlier.[5] The pure α form of IMC (5 g) was dissolved in 50 mL of ethanol in a 100-mL glass beaker. The temperature was maintained in a water bath at 37°C. The IMC suspension samples were withdrawn at appropriate time intervals, filtered, and dried under a vacuum at room temperature.[5] The UIM were sieved using 52- and 125-μm screens as described above. The mixture of UIM and excipient (UIEM) was obtained by mixing the UIM with 50% of the excipient mixed powder, and the tablet (UIEMT) of UIEM was compressed as described above. The contents of α and γ forms were determined by using x-ray powder diffraction and NIR spectroscopy. All data were reported as the average of 5 runs, respectively.

RESULTS AND DISCUSSION

Characterization of Form α and Form γ IMC

Figure 1 shows the x-ray powder diffraction profiles of the polymorphic forms of IMC, additives, and SIEM. The main x-ray powder diffraction peaks of the form γ (**Figure 1A**) were at 11.6, 16.8, 19.6, 21.8, and 26.6° (2θ), and those of the form a (**Figure 1B**) were at 8.4, 14.4, 18.5, and 22.0° (2θ), as reported previously.[5] The diffraction profile of form α was broader than that of form γ, which might be related to the lower crystallinity of form α. The lactose (**Figure 1E**) showed x-ray powder diffraction patterns due to crystalline α-lactose monohydrate, but cornstarch (**Figure 1F**) and HPC (**Figure 1G**) showed halo patterns due to noncrystalline solids. The x-ray powder diffraction profile of the SIEM with 0% γ form content (**Figure 1C**) showed peaks at 8.4, 14.4, 18.5, and 22.0° (2θ) due to form α, and those of the SIEM with 100% γ form content (**Figure 1D**) showed peaks at 11.6, 16.8, 19.6, 21.8, and 26.6° (2θ) due to form γ. The results suggested that polymorphic determination was possible by conventional x-ray powder diffraction in the mixed pharmaceutical preparations.

Figure 2 shows the DSC profiles of the pure form α and form γ of IMC. These DSC curves showed corresponding endothermic peaks at 155 and 162°C, respectively, which are attributable to sample melting, as reported previously.[21] These results suggested that the form α and form γ of IMC used in the present study were highly pure. Form α was enantiotropic form, but form γ was monotropic form.

Measurement of IMC Polymorphic Content in the SIEM and SIEMT by Conventional X-ray Powder Diffractometry

The x-ray powder diffraction profiles showed 2 main causes of fluctuation in the determination of crystal content: (1) intensity fluctuation of the x-ray direct beam during measurement, and (2) crystal orientation when the sample powder was loaded in the sample holder. To avoid fluctuation of direct beam intensity, the peak at 2θ = 28.8° of silicon powder was measured as an external standard for correction of the value of crystalline content. The calibration curve for measuring the SIEM with 0% to 100% γ form content by conventional x-ray powder diffraction was based on the total intensity of the 4 specific diffraction peaks, 2θ = 11.6, 19.6, 21.8, and 26.6°. The 4 diffraction peaks with high intensity were measured to minimize systematic error due to crystal orientation. The obtained calibration

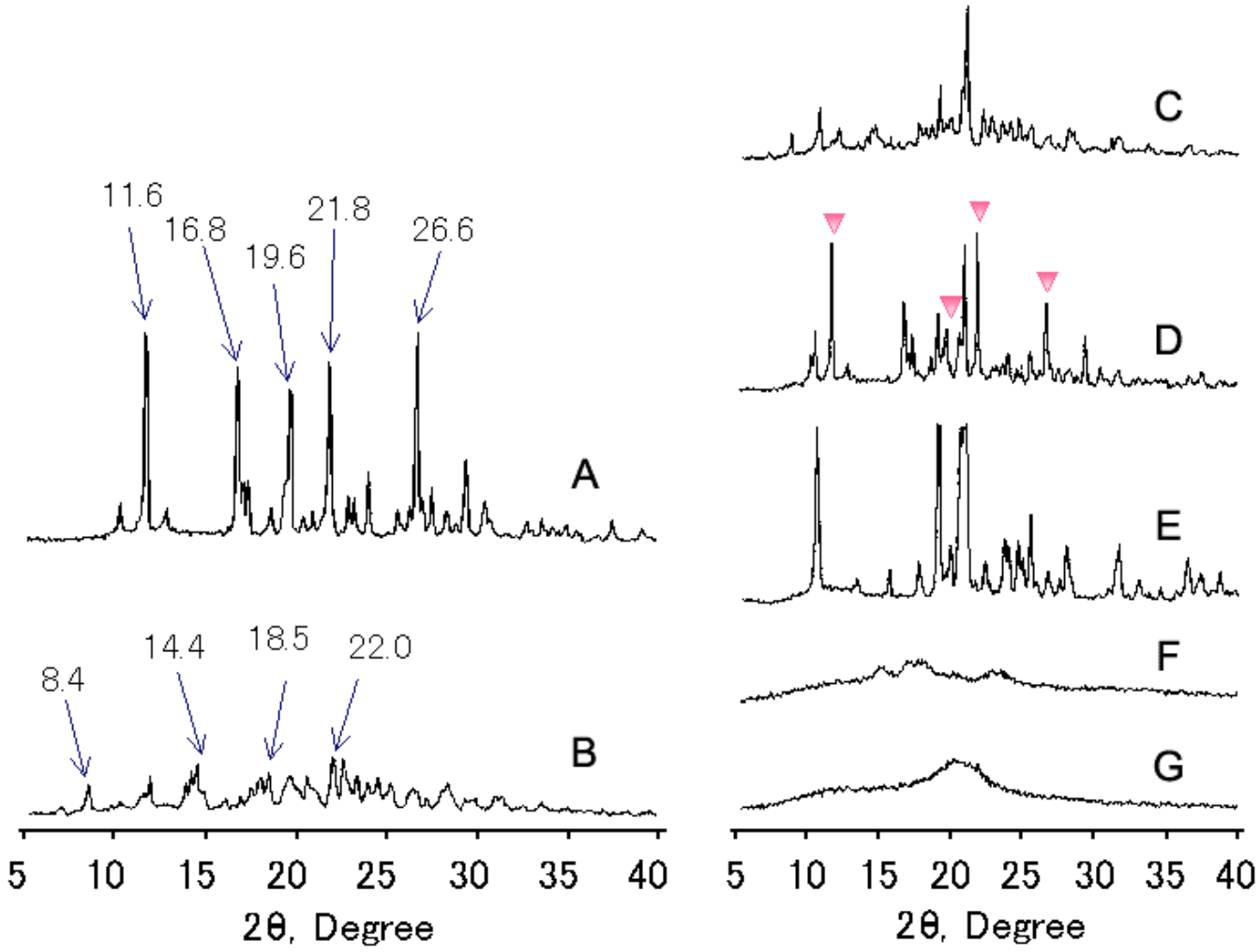

Figure 1. X-ray powder diffraction patterns of pure IMC polymorphous crystals, pharmaceutical ingredients, and SIEM: (A) γ form IMC, (B) α form IMC, (C) SIEM with 100% α form, (D) SIEM with 100% γ form, (E) lactose, (F) corn starch, (G) HPC. Triangles in d represent the significant peaks due to γ form.

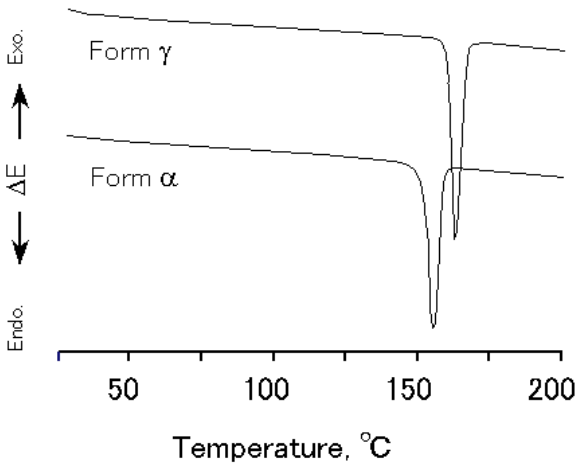

Figure 2. DSC curves of form α and form γ IMC (reported previously in Otsuka et al[12]).

curve to evaluate the polymorphic content of form α and γ ratio IMC in the SIEM measured using x-ray powder diffraction and the plot of total peak high intensity of 4 specific peaks against the form γ concentration was linear, with a slope of 0.011, an intercept of 0.028, and a correlation coefficient constant of 0.986 by the least-squares method. The polymorphic content in the SIEM was calculated based on this calibration curve. **Figure 3** shows a plot of the relation between the actual and predicted polymorphic contents of the SIEM measured using x-ray powder diffraction. This plot shows a linear relation. It has a slope of 0.960, an intercept of 0.011, and a correlation coefficient of 0.970. However, it has slightly higher 95% confidence levels for the prediction of individual y values and 95% confidence intervals of regression, indicating that x-

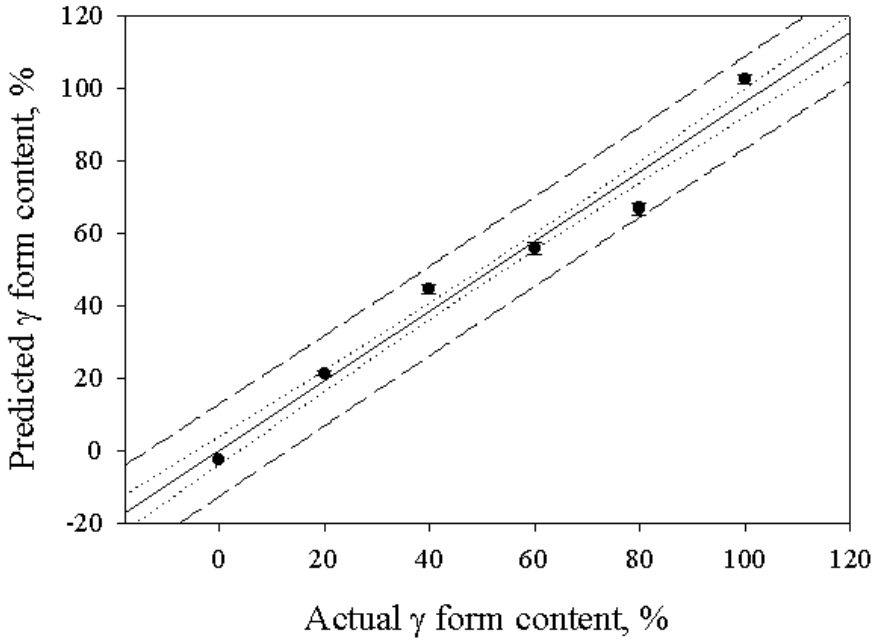

Figure 3. Relationship between the actual and predicted content of form γ IMC in the SIEM obtained by conventional x-ray powder diffractometry. The symbols and error bars present average and SD (n = 5). The solid line, long dashed line, and dotted line represent a regression line, 95% predicted interval, and 95% confidence interval, respectively.

raypowder diffraction has relatively low accuracy in the determination of crystalline content

Measurement of IMC Polymorphic Content in the SIEM and SIEMT by Chemoinfometric NIR Spectroscopy

Figure 4A shows the NIR spectra of the α and γ forms of IMC. The form α and form γ IMC showed significant NIR spectral peaks. The NIR absorption peaks of IMC were assigned.[21] The absorption peaks at 1130 and 1180 nm are associated with a second overtone of CH stretching bands for the HC=CH group and the aromatic ring, respectively. The peak at 1400 nm is associated with a second overtone of the CH stretching band. The absorption peaks at 1665, 1700, and 1730 nm are associated with the first overtone of CH stretching of the CH=CH group, the second overtone of the CH_3 group, and the first overtone of CH stretching bands of the CH_3 group. The peak at 2145 is associated with a combination tone of the NH and C=O groups' stretching bands, respectively. The peaks at 1665, 1700, and 1730 nm, and the baseline at around 1800 nm, of form γ were higher than those of form α, but the peak at 2200 nm was lower.

Figure 4B shows the NIR spectra of the excipients lactose, starch, and HPC. All NIR spectra of excipients showed significant NIR spectral peaks and were significantly different from those of form α and form γ IMC.

Figures 5A and **5B** show the NIR spectra of the SIEM with 0% to 100% γ form content and the SIEMT with 0% to 100% γ form content. The peak intensities at 1700, 1730, 1800, and 2200 nm of both spectra of the SIEM and the SIEMT decreased with increasing of form γ content. Therefore, the NIR spectra data were applied to PCR analysis to establish a quantitative model to evaluate the polymorphic content in complex pharmaceutical preparations.

PCR is presented as regression of Y on selected principal components of X. Properties of PCR are given together with a discussion on selection of eigenvectors. Since PCR is useful to understanding the relationship between the objective parameters and the principal component in the spectra, PCR was applied to the present study.

A spectrum including *n* spectral data can be seen as a point in an *n*-dimensional space. In multivariate data analysis, PCA/PCR of a spectral data matrix is a basic

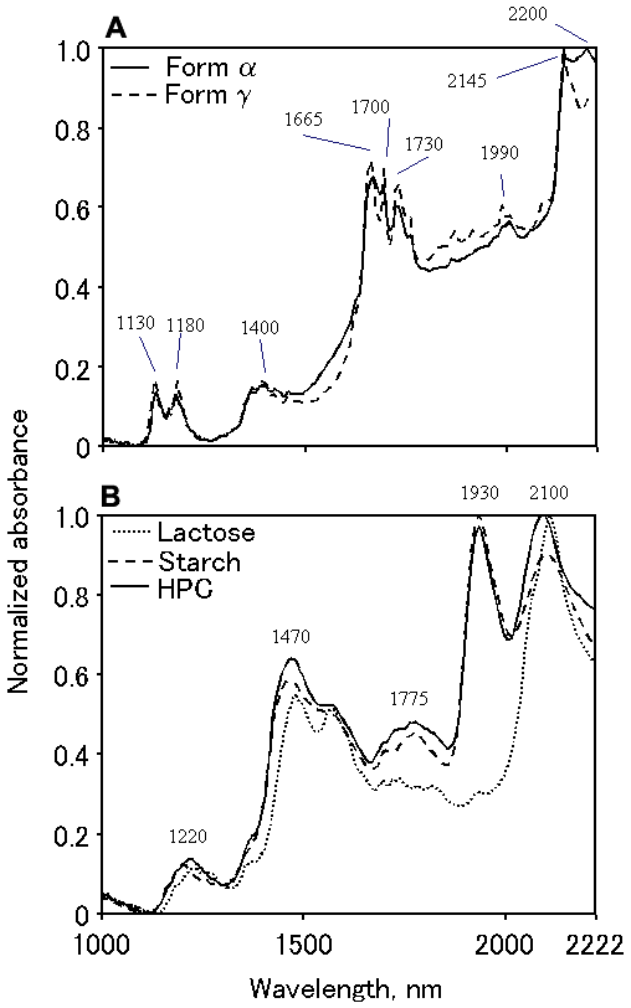

Figure 4. NIR spectra of form a and form γ IMC and pharmaceutical ingredients. The spectra were transformed by peak normalization method: (A) polymorphous IMC, (B) additives.

tool. PCA/PCR decomposes X into a score matrix T times a loading matrix P' plus a residual matrix E[18]:

$$X = t_1 p'_1 + t_2 p'_2 + \cdots + E = TP' + E \qquad (1)$$

This decomposition is particularly useful for converting E to a few information plots (score plots and loading plots) and for modeling the systematic structure in E.

The NIR spectra for SIEM and SIEMT were performed as a pretreatment to minimize experimental error by using transformations of absorbance, peak high-normalized absorbance, and second derivative. The best conditions were determined to minimize the root mean squared error of prediction (SEP, Equation 2).

$$SEP = \sqrt{\frac{\sum (y_p - y_r)^2}{n}} \qquad (2)$$

where y_p is property value of prediction, y_r is property value of reference, and n is number of spectra in the calibration set.

Table 1 shows that SEPs of the correlation curves were calculated based on the 6 spectral data for training/test set corrected by 3 transformations. As a result, the minimum SEP value was calculated from normalized NIR spectra based on the 3–principal component model after normalization. The multiple correlation coefficient constant, the standard error of estimate, and the SEP of calibration models including 3 principal components were calculated and are summarized in **Table 1**.

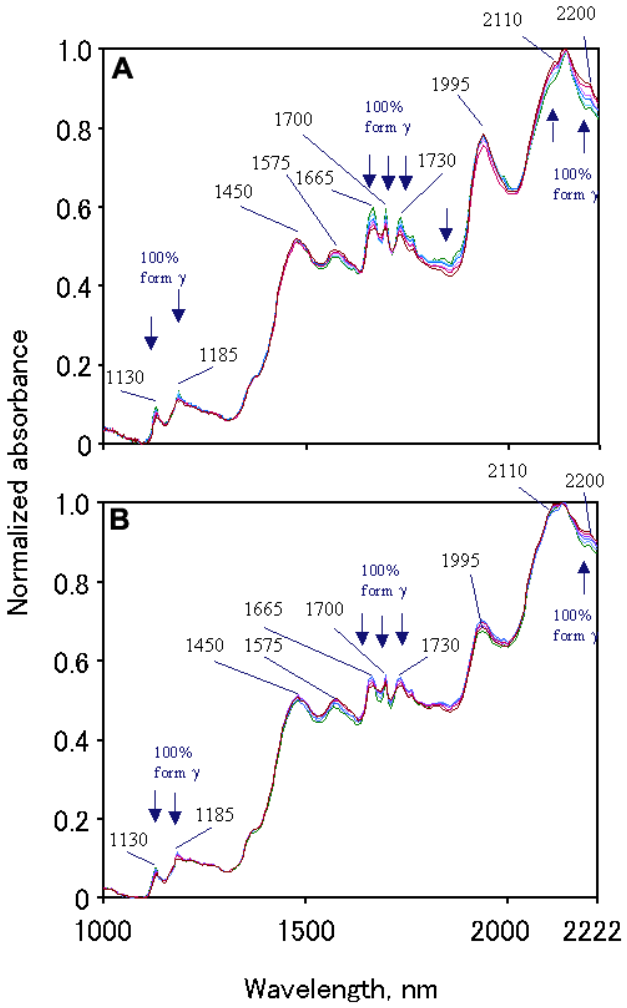

Figure 5. NIR spectra of (A) SIEM and (B) SIEMT. The spectra were transformed by peak normalization method.

Table 1. Confidence Limit of Correlation Calculated by Principal Component Regression Based on 3 Transformations and 3 Factors*

	SIEM	SIEMT
Transformation (SEP, based on 3 factors)		
Absorbance	6.378	26.62
Normalization	3.146	1.943
Second derivative	4.295	3.193
Normalization treatment (based on 3 factors)		
Multiple correlation coefficient	0.997	0.997
Standard error of estimate	2.929	2.872
Standard error of prediction	3.146	1.943

*SIEM indicates standard indomethacin/excipient mixture; SIEMT, standard indomethacin/excipient mixture, tablet form; SEP, squared error of prediction

Figure 6 shows the plots of the calibration data for the SIEM and SIEMT obtained by NIR spectroscopy based on the 3–principal components model between the actual and predicted values, respectively. The relationships between the actual and predicted polymorphic contents of SIEM and SIEMT show a straight line with a slope of 0.995 and 0.997, an intercept of 0.525 and –0.142, and a correlation coefficient constant of 0.993 and 0.995, respectively; predicted values were reproducible and had small SDs.

Figures 7 and **8** show loading vectors corresponding to the principal component (PC) of SIEM and SIEMT, respectively. In the PC1 of SIEM, there are positive peaks at 2187, 1934, 1711, and 1680 nm, and negative peaks at 1869, 1732, 1697, 1663, 1653, and 1185 nm. In PC2, there are positive peaks at 1989, 1920, 1729, 1697, 1663, 1653, 1185, and 1128 nm, and negative peaks at 2187, 2110, and 1581 nm. On the other hand, in the PC1 of SIEMT, there are positive peaks at 2187, 2003, 1938, 1769, 1711, and 1680 nm, and a negative peak at 2110 nm. In PC2, there are positive peaks at 2187 and 1680 nm, and negative peaks at 2142, 1989, 1869, 1758, 1729, 1697, 1663, 1653, 1185, and 1128 nm. The SEPs of PC1, PC2, and PC3 of SIEM were 20.05, 6.843, and 3.602, but those of SIEMT were 37.96, 9.797, and 3.491, respectively. The SEPs decreasing of SIEM and SIEMT were more significant at PC1 and PC2 than that between PC2 and PC3, respectively. This result indicated that PC1 loading vector of SIEM was more effective on the calibration model than that of SIEMT, and that PC2 of SIEM was less than that of SIEMT. The pattern of PC1 loading vector of SIEM was similar to PC2 of SIEMT, except for the peak at 1934 nm. On the other hand, the peak intensities at 2142, 1989, 1869, 1758, 1729, 1697, 1663, 1653, 1185, and 1128 nm decreased with decrease of form γ content in original spectra of SIEM and SIEMT (**Figures 5A** and **5B**), but those at 1680 and 2187 nm increased. The peaks in the loading vector of SIEM and SIEMT were reflecting a change of absorption peak intensity. The fact that SEP decreased indicated that the PC1 loading vector was the most important factor in the calibration model of SIEM, and PC2 was that of SIEMT. The result suggested that the loading vectors reflected the spectral difference between α and γ forms. The calibration model difference between SIEM and SIEMT based on the loading vectors might be reflected in powder structure change during tableting compression, such as porosity, mean particle size, and distribution in the powder bed.

Since the purpose of this study was to compare the accuracy of quantitative NIR spectroscopy to evaluate polymorphic content in the SIEM with that of conventional x-ray powder diffraction, the mean accuracy (A_m) and the mean precision (P_m) were determined by Equations 3 and 4, respectively:

$$A_m = \frac{\sum_{i=1}^{n} \frac{(X_c - X_t)}{X_t}}{n} \quad (3)$$

$$P_m = \frac{\sum_{i=1}^{n} \frac{|X_c - X_t|}{X_t}}{n} \quad (4)$$

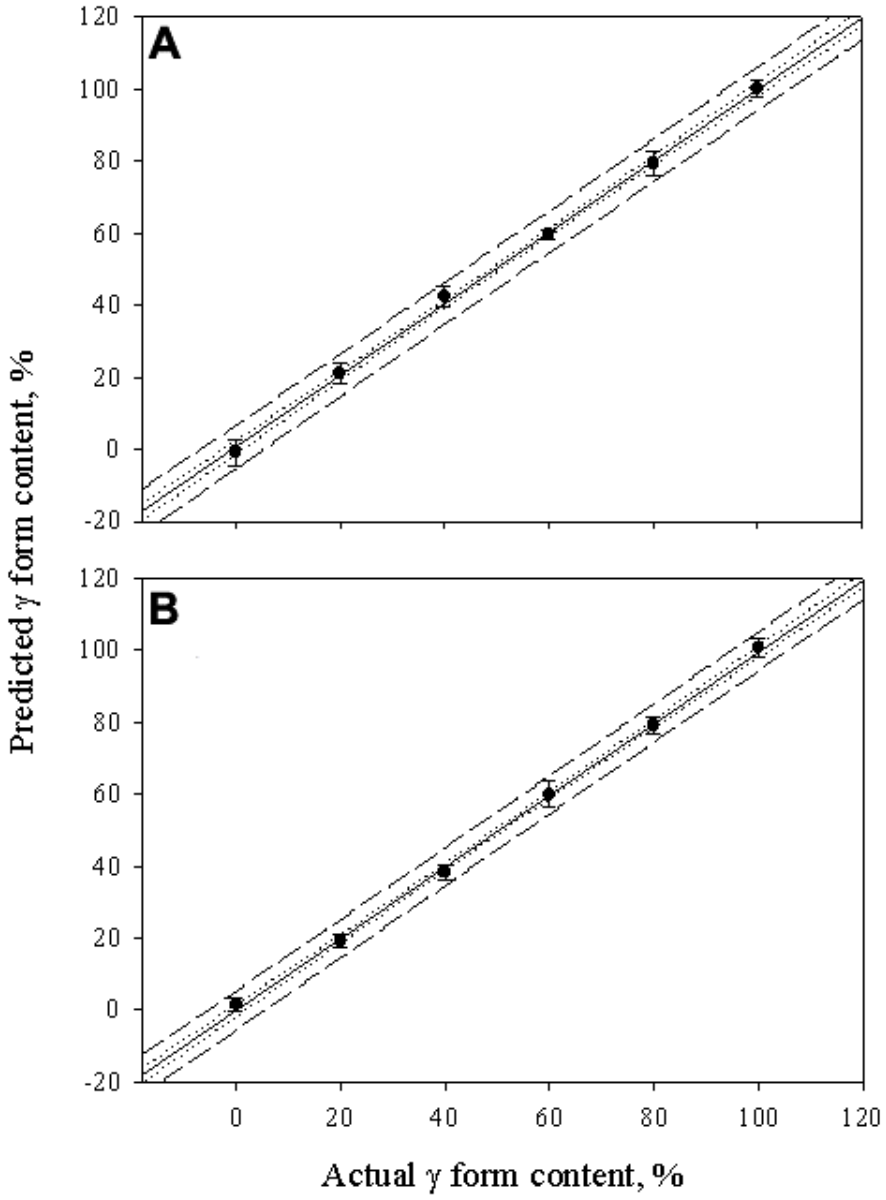

Figure 6. Correlation between actual and predicted content of form γ IMC in (A) SIEM and (B) SIEMT obtained by NIR spectroscopy. The symbols and error bars present average and SD (n = 5). The solid line, long dashed line, and dotted line represent a regression line, 95% predicted interval, and 95% confidence interval, respectively.

where X_c is predicted value of content of form γ IMC, X_t is actual value of content of form γ IMC, and n is number of experiments. The A_m and P_m for the SIEM and SIEMT evaluated by NIR spectroscopy and x-ray powder diffraction are summarized in **Table 2**. The confidence levels for the prediction of individual y values for the SIEM and SIEMT by NIR spectroscopy were much narrower than for the conventional x-ray method, but the result was consistent with the x-ray method. These results indicate that NIR spectroscopy has good linearity (shown in **Figures 7** and **8**) and good precision and accuracy (shown in **Table 2**). On the other hand, the x-ray method has good accuracy (shown in **Table 2**), but its linearity and precision (shown in **Figure 4**) are not as good. Thus, these assays are found to be superior for quantitative analysis of IMC polymorphs in the SIEM and SIEMT.

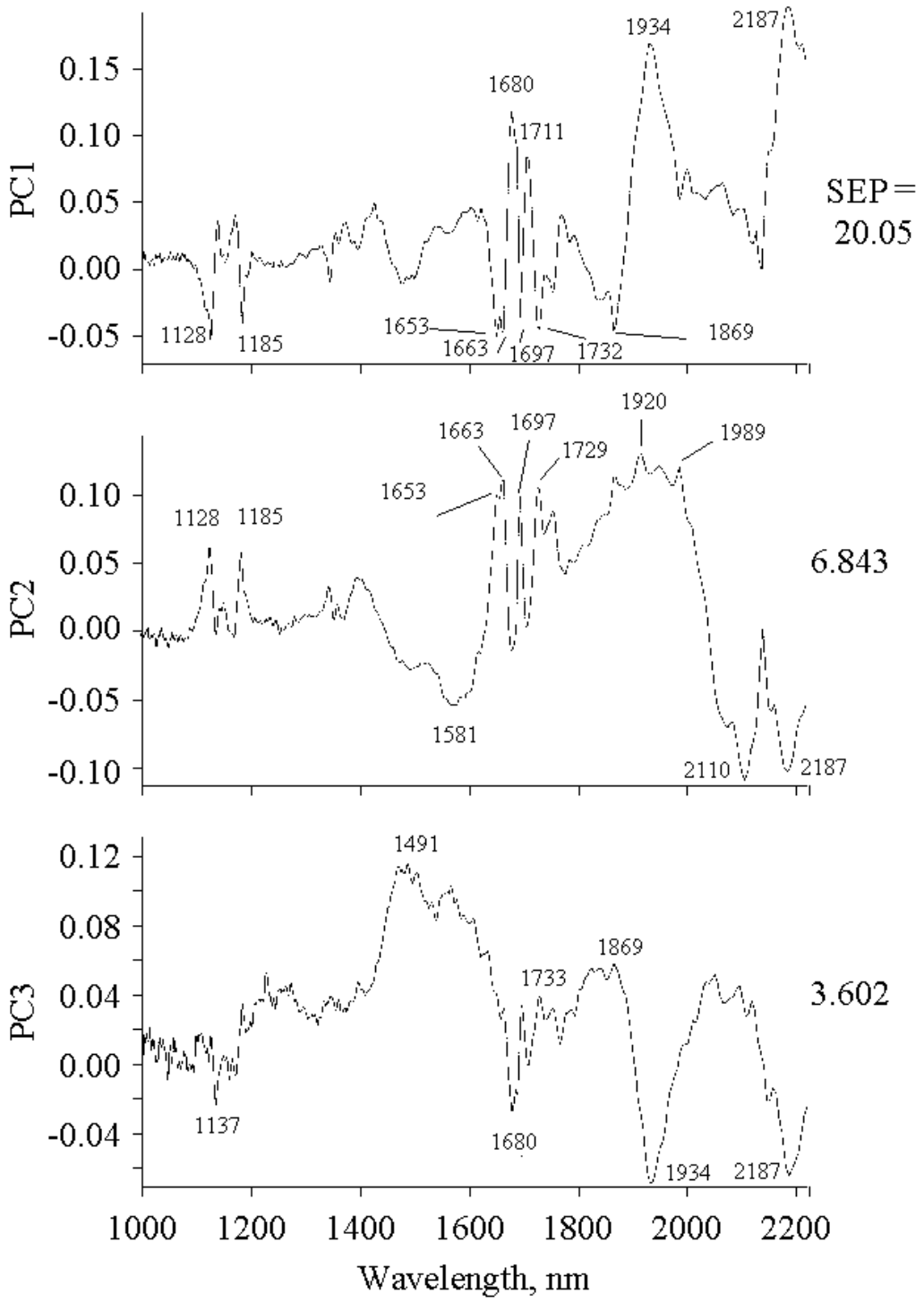

Figure 7. Loading vectors of PCs 1, 2, and 3 based on normalized NIR spectra of the SIEM calculated by PCR.

Comparative Evaluation of UIEM and UIEMT by Chemometric NIR Spectroscopy and Conventional X-ray Powder Diffraction

To check adequacy of the calibration models obtained in the above section, the polymorphic content of UIEM and UIEMT were evaluate by NIR spectroscopy and x-ray powder diffraction. **Figure 9** shows the plots of the predicted form γ content in the UIEM and UIEMT measured by x-ray powder diffractometry against those by NIR spectroscopy, respectively. The relationships between the predicted polymorphic contents of UIEM and UIEMT measured by x-ray powder diffraction and NIR spectroscopy show a straight line with a slope of

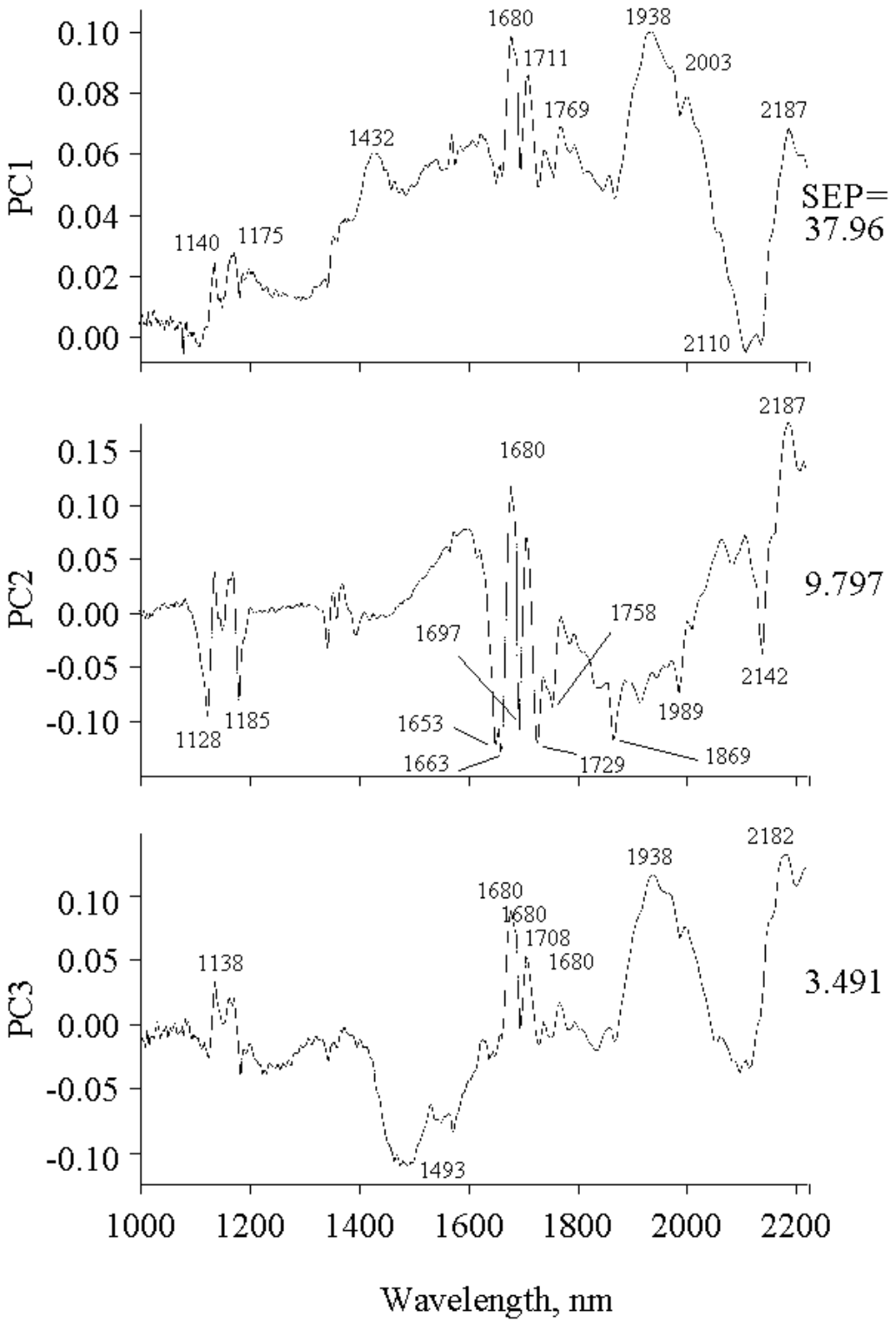

Figure 8. Loading vectors of PCs 1, 2, and 3 based on normalized NIR spectra of the SIEMT calculated by PCR.

1.306 and 1.328, an intercept of –7.625 and –21.43, and a correlation coefficient constant of 0.894 and 0.818, respectively. The slopes of the plots of UIEM and UIEMT were slightly different from those of SIEM and SIEMT, and the difference between UIEM and SIEM might be related to crystallinity or particle size during crystalline transformation of UIM, since the x-ray powder diffraction was affected by crystallinity and

Table 2. Mean Accuracy and Precision of Calbration Model for Evaluated Polymorphic Content in the SIEM and the SIEMT*

Method	Accuracy	Precision
XRPD	-0.00566	0.0734
NIR SIEM	0.0172	0.0405
NIR SIEMT	-0.0154	0.0386

*SIEM indicates standard indomethacin/excipient mixture; SIEMT, standard indomethacin/excipient mixture, tablet form; XRPD, x-ray powder diffraction; NIR, near infrared.

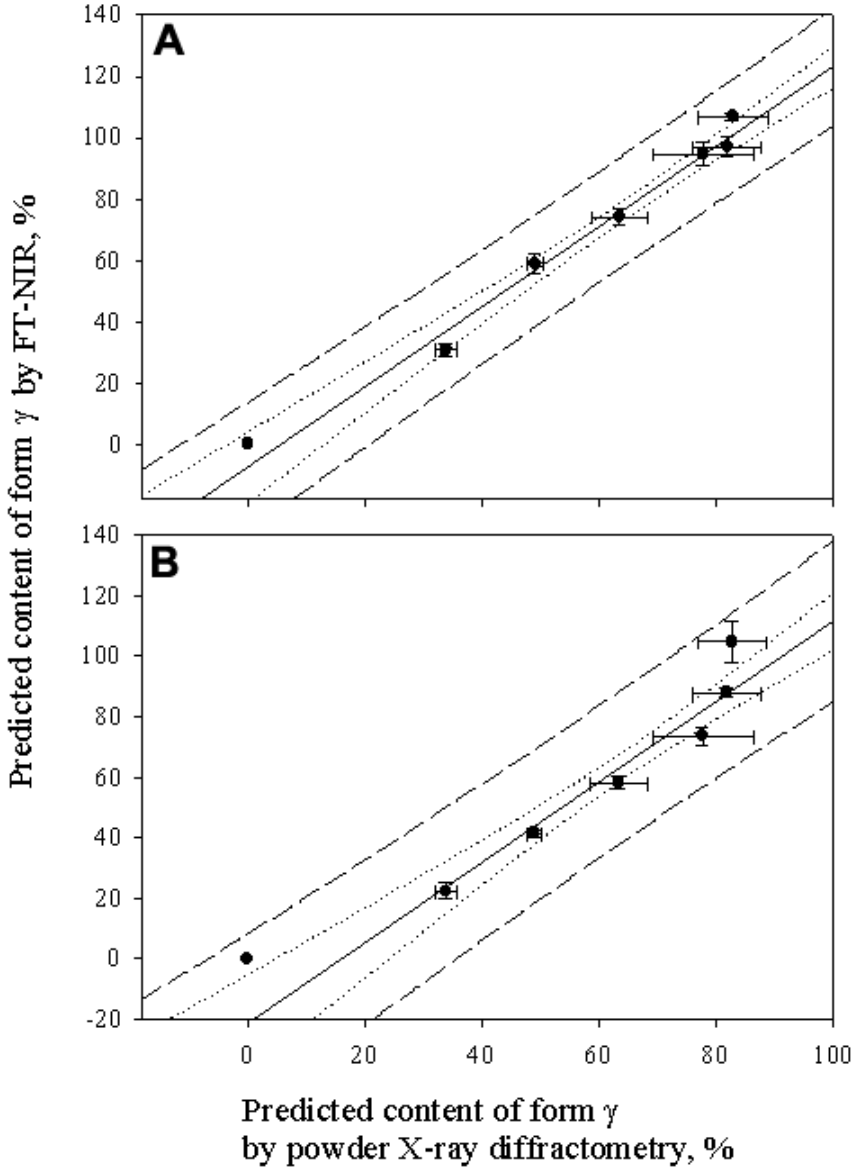

Figure 9. Relation between predicted form γ in the (A) UIEM and (B) UIEMT obtained by powder x-ray diffractometry and NIR spectroscopy. The symbols and error bars present average and standard deviation (n = 5). The solid line, long dashed line, and dotted line represent a regression line, 95% predicted interval, and 95% confidence interval, respectively.

particle size. However, the line represents a satisfactory correlation between the 2 predicted values of form γ IMC content in the UIEM and UIEMT. Thus, NIR spectroscopy is an effective method for quantitatively evaluating polymorph content in the UIEM and UIEMT.

CONCLUSION

Quantitative evaluation of IMC polymorphs in practical pharmaceutical systems, such as mixed powder and tablet systems, by NIR spectroscopy with the chemometric method was proven to be superior to conventional x-ray powder diffractometry. NIR spectroscopy could be of use as a validation method in the pharmaceutical industry—both in line production and in evaluating final pharmaceutical products.

REFERENCES

1. FDA Papers. Guidelines: manufacturing and controls for INDs and NDAs. Pharm Tech Japan. 1985;1:835-850.

2. Haleblian JK. Characterization of habits and crystalline modification of solids and their pharmaceutical applications. J Pharm Sci. 1975;64:1269-1288.

3. Otsuka M, Matsuda Y. Polymorphism, pharmaceutical aspects. In: Swarbrick J, Boylan JC, eds. Encyclopedia of Pharmaceutical Technology. Vol 12. New York, NY: Marcel Dekker; 1995:305-326.

4. Yoshino H, Hagiwara Y, Kobayashi S, Samejima M. Estimation of polymorphic transformation degree of pharmaceutical raw materials. Chem Pharm Bull. 1984;32:1523-1536.

5. Kaneniwa N, Otsuka M, Hayashi T. Physicochemical characterization of indomethacin polymorphs and the transformation kinetics in ethanol. Chem Pharm Bull. 1985;33:3447-3455.

6. Ahmed H, Buckton G, Rawlins DA. The use of isothermal microcalorimetry in the study of small degree of amorphous content of a hydrophobic powder. Int J Pharm. 1996;130:195-201.

7. Black DB, Lovering EG. Estimation of the degree of crystallinity in digoxin by X-ray and infrared methods. J Pharm Pharmacol. 1977;29:684-687.

8. Taylor LS, Zografi G. The quantitative analysis of crystallinity using FT-raman spectroscopy. Pharm Res. 1998;15:755-761.

9. Berridge JC, Jones P, Roberts-McIntosh AS. Chemometrics in pharmaceutical analysis. J Pharm Biomed Anal. 1991;9:597-604.

10. Edlund U, Grahn H. Multivariate data analysis of NMR data. J Pharm Biomed. Anal. 1991;9:655-658.

11. Lincoln D, Fell AF, Anderson NH, England D. Assessment of chromatographic peak purity of drugs by multivariate analysis of diode-array and mass spectrometric data. J Pharm Biomed Anal. 1992;10:837-844.

12. Otsuka M, Kato F, Matsuda Y. Comparative evaluation of the degree of indomethacin crystallinity by chemoinfometrical Fourier-transformed near-infrared spectroscopy and conventional powder X-ray diffractometry. PharmSci. 2000;2, Article 9.

13. Morisseau KM, Rhodes CT. Near-infrared spectroscopy as a nondestructive alternative to conventional tablet hardness testing. Pharm Res. 1997;14:108-111.

14. Drennen JK, Lodder RA. Nondestructive near-infrared analysis of intact tablets for determination of degradation products. J Pharm Sci. 1990;79:622-627.

15. Buchanan BR, Baxter MA, Chen TS, Qin XZ, Robinson PA. Use of near-infrared spectroscopy to evaluate an active in a film-coated tablet. Pharm Res. 1996;13:616-621.

16. Frake P, Gill I, Luscombe CN, Rudd DR, Waterhouse J, Jayasooriya UA. Near-infrared mass median particle size determination of lactose monohydrate, evaluating several chemometric approaches. Analyst. 1998;123:2043-2046.

17. Martents H, Næs T. Multivariate Calibration. New York, NY: John Wiley & Sons; 1989.

18. Norris T, Aldridge PK, Sekulic SS. Determination of end-points for polymorph conversions of crystalline organic compounds using on-line near-infrared spectroscopy. Analyst. 1997;122:549-552.

19. Saver RW, Meulman PA, Bowerman DK, Havens JL. Factor analysis of infrared spectra for solid-state forms of delavirdine mesylate. Int J Pharm. 1998;167:105-120.

20. Patel AD, Luner PE, Kemper MS. Low-level determination of polymorph composition in physical mixtures by near-infrared reflectance spectroscopy. J Pharm Sci. 2001;90:360-370.

21. Otsuka M, Kato F, Matsuda Y. Determination of indomethacin polymorphic contents by chemometric near-infrared spectroscopy and conventional powder X-ray diffractometry. Analyst. 2001;126:1578-1582.

22. Blanco M, Villar A. Polymorphic analysis of a pharmaceutical preparation by NIR spectroscopy. Analyst. 2000;125:2311-2314.

23. Patel AD, Luner PE, Kemper MS. Quantitative analysis of polymorphs in binary and multi-component powder mixtures by near-infrared reflectance spectroscopy. Int J Pharm. 2000;206:63-74.