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Studies on the influence of uniformity of particle size of powder, tapping and sample replacement for diffusion reflectance quantitative NIR spectrometric analysis

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The extent of deviation factors and the influence of pre-processing of spectra for a quantitative application of reflectance NIR measurement against powder sample were examined. Lactose monohydrate (NGLM), a medical additive was used for this study. Ground lactose monohydrate (GLM) and NGLM were measured by NIR reflectance spectroscopy. In the wave number range from 12000 cm^{-1} to 4000 cm^{-1}, the ratios of absorbance values (a.v.) between the wave numbers of GLM and NGLM were almost the same and no influence of intensity of absorbance through the measurement range was observed concerning heterogeneity of particle size. Absorbance values of NGLM were decreased with increasing number of tapping without a bit difference of the change of a.v. The several statistical parameters of a.v. from both samples were estimated. The relative standard deviation (RSD) and 95% confidence intervals (CIs) of a.v. on successive measurements at a fixed position in GLM and NGLM vials were almost the same. However, the RSD and 95% confidence of absorbance value of NGLM were larger than these GLM, i.e., RSD: 0.66% for NGLM, 0.42% for GLM. The 95% of CI of NGLM was ten times larger than that of GLM in five replacement positions. The two kinds of baseline corrections, the SNV and MSC processing were examined to evaluate the extent of influence against a.v. The 95% CI calculated from a.v. by the SNV pre-processing showed a wider range compared with that from no pre-processing and MSC pre-processing. These results suggest that the statistical confidence of a.v. would also change by pre-processing. It is important to consider the statistical confidence of a.v. for precise quantitative application of the reflectance NIR spectroscopy.

1. Introduction

Near infrared (NIR) spectroscopic analysis has been used in the petroleum and the food industries to check qualities of the products. Recently, many pharmaceutical manufactures have introduced it in order to apply to manufacturing process control because the NIR analysis can be used in solid state of pharmaceuticals nondestructively. Especially, an application of NIR spectroscopic technology to a real-time analysis in the pharmaceutical manufacturing process has been tried (Hailey et al. 1996, Sekulic et al. 1998; Li and Worosila 2005; El-Hagrasy et al. 2001; Smith et al. 2002; Clarke 2004; Fevotte et al. 2004; Terashita and Nanba 2004; El Hagrasy et al. 2006). A number of pharmaceutical companies have challenged to use NIR spectrometry for manufacturing management and quality control. Several papers dealing with qualitative and/or quantitative application for pharmaceutics have been published (Dreassi et al. 1996).
However, NIR spectra shows mixed spectroscopic information of the sample depending on its composition, so we often use a mathematical method such as the chemometrics for the extraction of useful spectroscopic information (Dreassi et al. 1998).
Moreover, NIR spectra are influenced by characteristics of powder, for example, crystal shape, particle size (Ozaki 1998; O'Neil et al. 2003), tapping and materials of glass vials (Yoon et al. 1998). Powder characteristics would affect confidence about quantitative data obtained by NIR diffusion reflectance spectrometer. It is known that there are several deviation factors that would affect spectrum baseline, and these deviation factors would be removed by "pre-processing" which is achieved with one click of PC software. Mathematical data processing will give us reasonable results, but these results sometimes have unclear process, which is expressed as "the black box technique".
This paper describes the extent of influences of tapping and replacement of sample vial as deviation factors, and the effectiveness of pre-processing of spectra to achieve more precise quantitative NIR measurement.

2. Investigations and results

2.1. Spectrum pattern of GLM and NGLM

The NIR spectra of the lactose monohydrate (non-ground, NGLM, shown in solid line) and the ground lactose

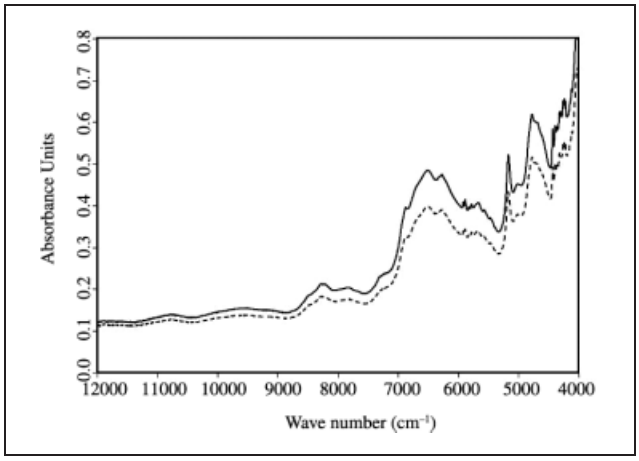

Fig. 1: Typical NIR spectra of lactose monohydrate (NGLM: solid line, GLM: broken line)

monohydrate (ground, GLM, shown in broken line) are shown in Fig. 1. The wave numbers giving chemical information of two compounds were presumed, and are shown in Table 1.

There was no difference between of spectrum pattern of GLM and NGLM except for a baseline absorbance. The absorbance of GLM was lower than that of NGLM. According to the presumed wave numbers (Table 1), the wave numbers of 5888 cm^{-1} and 4776 cm^{-1} were chosen for this study, because these wave numbers did not interfer with absorbance bands from other molecules such as water and have been observed clearly. Table 2 shows the differences of absorbance values (a.v.) of each characteristic wave number between GLM and NGLM. The extents of absorbance difference were expressed as the ratios of absorbance value of GLM divided by that of NGLM. All ratios of a.v. of each wave number were almost same.

2.2. Influence of the tapping against a.v.

The changes of a.v. depending on the number of tapping in both LMs are shown in Table 3. Figure 2 shows the relationship between a.v. and the number of tapping of both samples at two kinds of wavenumbers. From these results, the a.v. of NGLM was decreased from 0 to 5 (5888 cm^{-1}) or to 10 (4776 cm^{-1}) tapping, and the change in a.v. showed a steady state in more than 10 tapping. In case of GLM, the absorbance seemed to be gradually increased to 30 tapping. These results suggest that the bulk of powder with a wide range of particle size and/or shape (e.g. NGLM) would be packed by tapping. Generally, a more packed sample gives lower absorbance. The changes of absorbance showed same profile in both wave numbers.

2.3. Influence of heterogeneity of particle size on precision of measurement

2.3.1. Influence of successive sample measurements on fixed sample position

NGLM and GLM after cumulative 50 tapping were successively measured as often as fifteen times to estimate an influence of powder bulk against a spectroscopic precision. The columns of raw absorbance in Table 4 and 5 show the a.v. of both samples at 5888 cm^{-1}. The average, standard deviation (SD) and relative standard deviation (RSD) of a.v. were 0.4130, 1.68×10^{-4} and 0.039% for NGLM and 0.3448, 1.40×10^{-4} and 0.042% for GLM, respectively. The RSDs of both a.v. were almost the same. These results suggest that there is no significant difference for precision of a.v. between NGLM and GLM under this condition (fixed position).

Furthermore, to gain a detailed statistical estimation, CIs of both data sets were calculated. The calculation method is described as mentioned below.

95% CI of estimated population average of a.v. = Average of a.v. $\pm$ t (φ, 0.05) $\sqrt{(V/N)}$ (Both sides)

V: Variance = Sum of square/(n $-$ 1), Sum of square: $\sum (X_i - X_{ave.})^2$, 95% CI of estimated population average of a.v. of NGLM = $0.4130 \pm 9.330 \times 10^{-5}$, 95% CI of estimated population average of a.v. of GLM = $0.3448 \pm 8.4938 \times 10^{-5}$.

Each 95% CI of population average was very narrow, and these results indicate that the heterogeneity in particle size

Table 1: Presumed characteristic wave numbers of lactose monohydrate

8286 cm^{-1}	6874 cm^{-1}	6508 cm^{-1}	5921 cm^{-1}	5888 cm^{-1}	5169 cm^{-1}	4776 cm^{-1}
Second overtone of CH_2	Absorption of H_2O	Overtone of Stretching Vibration of OH	First overtone of $CH(CH_2)$	First overtone of $CH(CH_2)$	First overtone of $CH(CH_2)$	Combination of OH

Table 2: Differences of the ratio of absorbance values of each characteristics wave numbers between the GLM and NGLM

	8286 cm^{-1}	6874 cm^{-1}	6508 cm^{-1}	5921 cm^{-1}	5888 cm^{-1}	5169 cm^{-1}	4776 cm^{-1}
NGLM (Absorbance value)	0.2103	0.3843	0.4691	0.3978	0.4036	0.5053	0.5972
GLM (Absorbance value)	0.1800	0.3209	0.3905	0.3334	0.3383	0.4262	0.5075
Ratio (G/N)	0.86	0.84	0.83	0.84	0.84	0.84	0.85

Table 3: Changes of absorbance values against number of tapping of the NGLM and GLM

	Number of Tapping	0	1	5	10	20	30	40	50
NGLM (Absorbance value)	5888 cm^{-1}	0.4273	0.4186	0.4149	0.4138	0.4127	0.4167	0.4149	0.4149
	4776 cm^{-1}	0.6469	0.6331	0.6263	0.6234	0.6206	0.6238	0.6211	0.6211
GLM (Absorbance value)	5888 cm^{-1}	0.3386	0.3394	0.3421	0.3436	0.3447	0.3476	0.3468	0.3473
	4776 cm^{-1}	0.5128	0.5132	0.5153	0.5168	0.5175	0.5205	0.5192	0.5194

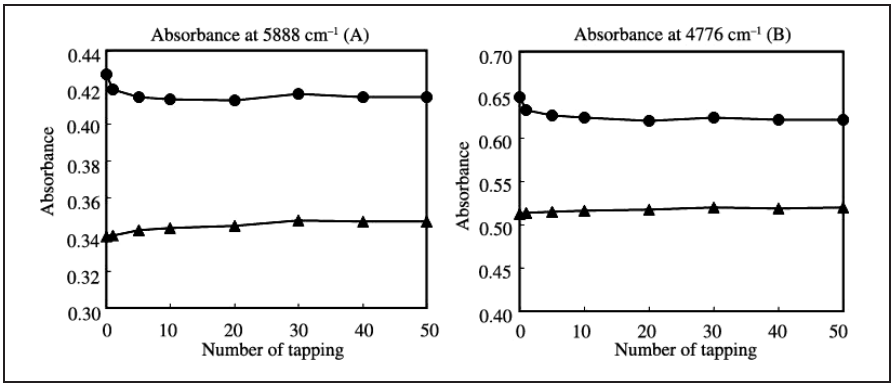

Fig. 2:
Relationship between absorbance values and number of tapping of the NGLM and the GLM (A: absorbance at 5888 cm^{-1}, B: absorbance at 4776 cm^{-1})

Table 4: Absorbance values of the NGLM after SNV and MSC pre-processing at successive 15 times measurements of fixed position of sample vial

GLM (Fixed position)	Raw absorbance	SNV processed absorbance value	MSC processed absorbance value
1	0.4129	0.8101	0.3818
2	0.4131	0.8106	0.3818
3	0.4131	0.8105	0.3818
4	0.4132	0.8105	0.3818
5	0.4129	0.8092	0.3816
6	0.4132	0.8098	0.3817
7	0.4130	0.8095	0.3817
8	0.4129	0.8098	0.3817
9	0.4131	0.8112	0.3819
10	0.4129	0.8103	0.3818
11	0.4130	0.8102	0.3818
12	0.4727	0.8105	0.3818
13	0.4130	0.8094	0.3817
14	0.4127	0.8105	0.3818
15	0.4132	0.8102	0.3818
Ave.	0.4130	0.8102	0.3818
SD	0.00016	0.00053	0.00007
RSD	0.039%	0.065%	0.019%

Table 5: Absorbance values of the GLM after SNV and MSC pre-processing at successive 15 times measurements of fixed position of sample vial

NGLM (Fixed position)	Raw absorbance	SNV processed absorbance value	MSC processed absorbance value
1	0.3447	0.7792	0.3771
2	0.3447	0.7785	0.3370
3	0.3448	0.7781	0.3769
4	0.3449	0.7786	0.3770
5	0.3451	0.7784	0.3769
6	0.3447	0.7779	0.3769
7	0.3446	0.7778	0.3769
8	0.3446	0.7780	0.3769
9	0.3449	0.7783	0.3769
10	0.3449	0.7780	0.3769
11	0.3446	0.7783	0.3768
12	0.3449	0.7776	0.3769
13	0.3447	0.7779	0.3769
14	0.3447	0.7782	0.3769
15	0.3447	0.7787	0.3770
Ave.	0.3448	0.7782	0.3769
SD	0.00014	0.00041	0.00007
RSD	0.042%	0.052%	0.019%

of powder has no influence for spectroscopic precision of NIR measurement when the sample is placed exactly in the same manner.

2.3.2. Influence of heterogeneity of particle size of powder for sample setting

In order to estimate a variance of a.v. by sample vial replacement, 50 tapped both samples were measured. An initial position was defined as 0 degree. Averages at 90, 180, 270 and 360 degree rotated from initial position were compared with initial a.v. Absorbance values, average values, SD and RSD which were obtained form NGLM and GLM at 5888 cm^{-1} of wave number are shown in Table 6.

The 95% CIs (CI) of population average of a.v. obtained by NIR measurement of NGLM and GLM were 0.4166 ± 0.0109 and 0.3469 ± 0.0018, respectively.

Table 6: Influence of sample replacement for absorbance values of the GLM and NGLM at 5888 cm^{-1} of wave number

Rotated position (degree)	0	90	180	270	360	Ave.	SD	RSD
NGLM (Absorbance value)	0.4150	0.4170	0.4179	0.4201	0.4129	0.4166	0.0028	0.66%
GLM (Absorbance value)	0.3480	0.3455	0.3482	0.3475	0.3451	0.3469	0.0015	0.42%

Table 7: Absorbance values of the NGLM after SNV and MSC pre-processing at 5 different positions of sample vial replacement

NGLM	Raw absorbance value	SNV processed absorbance value	MSC processed absorbance value
0	0.4150	0.8095	0.3817
90	0.4171	0.8146	0.3825
180	0.4180	0.8113	0.3819
270	0.4202	0.8135	0.3823
360	0.4147	0.8118	0.3820
Ave.	0.4170	0.8121	0.3821
SD	0.0023	0.0020	0.00032
RSD	0.54%	0.24%	0.08%

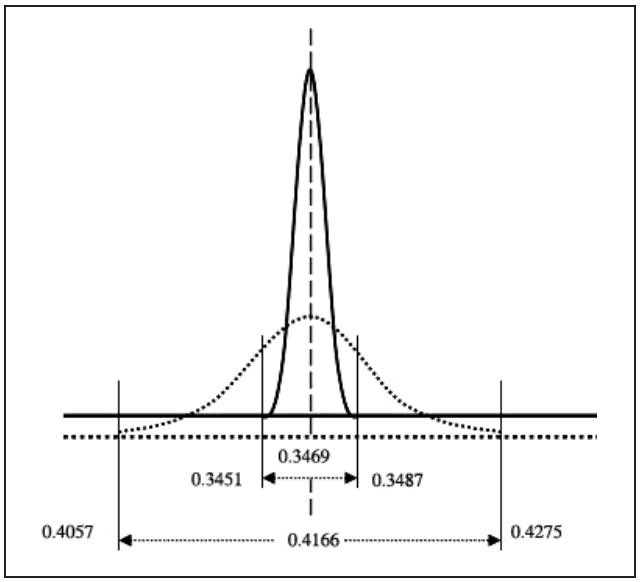

Fig. 3: Image of confidence intervals of population averages of absorbance values of the NGLM and the GLM

Figure 3 shows an image of both CIs of population averages. The 95% CI of a.v. of NGLM was approximately 10 times wider than that of GLM, in spite of small RSDs between the a.v. of NGLM and GLM. This fact suggests that heterogeneity of particle size would affect the statistical confidence of an absorbance value.

2.4. Influence of baseline correction ("pre-processing") for quantitative NIR analysis

The "pre-processing" by computer software will be useful when the spectral baselines are varied from several deviation factors. Two types of "pre-processing" such as Standard Normal Variate method (SNV) or Multiplicative scatter correction (MSC) are often used for correction of the base line. SNV pre-processing is characterized as algorithm correcting the baseline by using all wavenumber points of each spectrum. On the other hand, the MSC pre-processing is calculated by averaging all wave number points of a series of all spectra. The average by MSC pre-processing is characterized by the corresponding data set. Therefore, the results of the MSC pre-processing would not be suitable for application of new sample set.

The changes of a.v. against the number of tapping of three pre-processing conditions against NIR spectrum of GLM are shown in Fig. 4. The changes of a.v. obtained from these pre-processing algorithms showed almost the same profile. The changing ratios expressed as differences between the highest and the lowest a.v. obtained from the raw, SNV and MSC pre-processing data were 1.03, 1.01 and 1.00, respectively. In case of NGLM, the changing ratios of a.v. obtained from the SNV or MSC pre-processing were different from that was obtained from raw one. The downward profile of the change of a.v. up to 30 tapping was changed by the pre-processing of spectrum (Fig. 5), and the changing ratios of a.v. at 50 tapping calculated from the lowest to the highest a.v. after the SNV and MSC pre-processing were 1.01 and 1.00, respectively.

The RSDs and 95% CIs of a.v. at successive 15 measurements of fixed position are shown in Table 4 for NGLM and Table 5 for GLM, respectively. The RSD estimated from the a.v. calculated by the SNV pre-processing was larger than the others were. The MSC pre-processing gave the smallest RSD among three different types of pre-processing in both samples. The 95% CIs of a.v. in the same way were $0.4130 \pm 8.761 \times 10^{-5}$, $0.8102 \pm 28.64 \times 10^{-5}$ and $0.3818 \pm 4.361 \times 10^{-5}$ for NGLM, and $0.3448 \pm 8.005 \times 10^{-5}$, $0.7782 \pm 22.94 \times 10^{-5}$ and $0.3769 \pm 3.4841 \times 10^{-5}$ for GLM, respec-

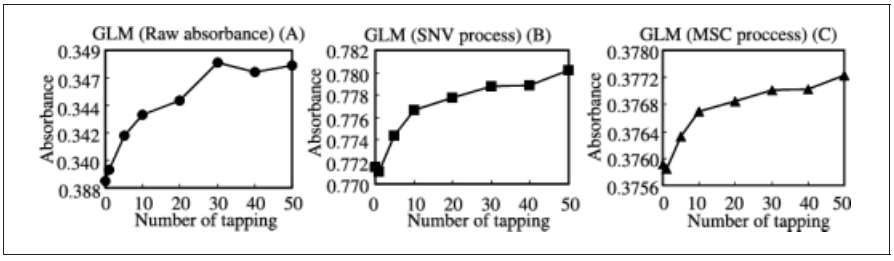

Fig. 4:
Changes of absorbance values against number of tapping of the GLM at 5888 cm^{-1} (A: raw absorbance values, B: SNV treated absorbance values, C: MSC treated absorbance values)

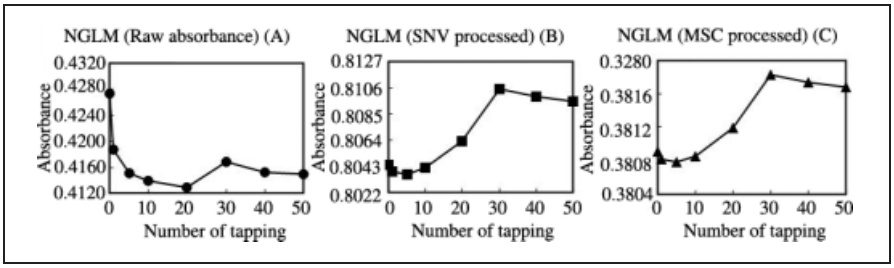

Fig. 5:
Changes of absorbance values against number of tapping of the NGLM at 5888 cm^{-1}
(A: raw absorbance values, B: SNV treated absorbance values, C: MSC treated absorbance values)

Table 8: Absorbance values of the GLM after SNV and MSC pre-processing at 5 different positions of sample vial replacement

GLM	Raw absorbance	SNV processed absorbance value	MSC processed absorbance value
0	0.3474	0.7802	0.3772
90	0.3455	0.7748	0.3764
180	0.3482	0.7762	0.3766
270	0.3475	0.7800	0.3772
360	0.3452	0.7780	0.3769
Ave.	0.3468	0.7778	0.3769
SD	0.0013	0.0024	0.00032
RSD	0.38%	0.30%	0.09%

tively. These results indicate that the SNV pre-processing tends to spread the CI of calculated a.v.

Tables 7 and 8 show the RSDs and the 95% CIs of the calculated a.v. from the vial replacement in both samples by three pre-processing. According to the comparison of the RSDs of a.v. between the spectrum converted by the SNV pre-processing and the raw spectrum, the RSD calculated from the a.v. after the SNV pre-processing was approximately a half of that of raw a.v. The RSDs of the a.v. after the MSC pre-processing were about 7 times lower than those of raw a.v. obtained from NGLM and 4 times lower than that from GLM, respectively. These phenomena are presumed that the MSC pre-processing will be able to achieve very low RSD because of the use of whole data set for the processing.

3. Discussion

Recently, a concept of Process Analytical Technology (PAT) for quality control is introduced in pharmaceutical industry. The diffusion reflectance NIR spectroscopy has been expected to apply not only for "the in-line and/or the on-line process analysis" but also for "the quality control test", because of its convenient, non-invasive and non-destructive techniques. Especially, the diffusion reflectance NIR spectrometry would be a popular method for application to qualitative and quantitative analysis because it could be used for a wider wave number range for sample measurements and various sample situations compared with transmittance NIR spectroscopic analysis. In this study, it was clearly shown that the number of tapping would affect a.v. in spite of the same measurement conditions, and particle size un-uniformity would give a variance of correlation between the number of tapping and absorbance. Therefore, characteristics of the diffusion reflectance NIR measurement for an appropriate quantitative analysis using a.v. should be scrutinized. The same patterns of NIR spectra should be obtained from the same ingredients in samples, but the a.v. would change by un-uniformity of particle size in the sample. From this study, the heterogeneity in particle size of powder did not influence the variance very much, but a significant change of the CI of a.v. was observed. It would be desirable to use ground powder with uniform particle size in order to obtain gain precise data.

Replacements of sample vial are often performed in usual experimental situation. However, replacements of vial would be one of variance factors of quantitative a.v. It is recommended that data should be obtained by replacing samples. Because sample vials would not be placed at the exact same position in practical applications, the condition of the bottom of vials or/and chemical components of glass would also affect the a.v. The deviation factors of absorbance such as replacement of vial position or use of different vials should be considered to prepare a calibration curve.

The approach described in this study is expected to provide evidence for giving a statistic confidence to quantitative values and for giving validity against control range of quantitative results for diffusion reflectance NIR spectroscopic quantitative analysis.

4. Experimental

4.1. Materials and instrument

Lactose monohydrate was purchased from Wako chemical Co. (Osaka, Japan). NIR measurement was performed using the MPA near infrared spectrophotometer (Bruker Optics K.K., Germany). Glass vials were purchased from Bruker Optics K.K. Measurement range, scan wave number interval, resolution and numbers of integration steps were 12000 to 4000 cm^{-1}, 2 cm^{-1}, 4 cm^{-1} and 32, respectively.

4.2. Sample preparation

Lactose monohydrate was dried in a decompressed desiccator for 2 h. A portion of lactose monohydrate was well manually ground in a mortar for 2 min. A suitable volume of the ground lactose monohydrate was put into a glass vial for NIR measurement. The other portion of unprepared lactose monohydrate (non-ground lactose monohydrate) was also put into a glass vial.

4.3. Measurement

All measurements were performed under the same condition as mentioned above. Each vial was tapped 0, 1, 5, 10, 20, 30, 40, 50 times cumulatively, and NIR measurement was performed at each tapping. The "tapping" was defined that the bottom of a glass vials was lightly tapped on the desk by hand. In order to estimate a spectroscopic precision of the NIR instrument, 15 times successive measurements at fixed position of glass vial, which was tapped cumulatively 50 times were carried out. Moreover, each vial was also measured at angles of 0, 90, 180, 270, 360 degree right-handed rotation to estimate the extent of deviation of vial replacement.

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BOOK REVIEWS

Lexikon der Pharma-Technologie. Werkstoffe und Verfahren

Von Georg Henkel, Frank Stieneker und Martin Wesch. Aulendorf 2007: Editio Cantor Verlag. 525 Seiten, 138,00 €

Neben dem schon lange etablierten Lexikon der Hilfsstoffe ist im Editio Cantor Verlag mit dem „Lexikon der Pharma-Technologie" jetzt ein weiteres pharmazeutisches Nachschlagewerk erschienen. Der Titel macht neugierig: Was ist wohl unter dem Begriff der „Pharma-Technologie" im Unterschied zu Pharmazeutischer Technologie oder zu Pharmatechnik zu verstehen? Unter dem Stichwort Pharma-Technologie findet sich im Lexikon der Pharma-Technologie ausschließlich ein Verweis auf Pharmazeutische Technologie. Der Eintrag zur Pharmazeutischen Technologie ist wie die meisten Begriffserläuterungen im Lexikon kurz und lautet: „Lehre von der Herstellung und Entwicklung der Arzneiformen – früher meist als Galenik bezeichnet. Moderne Pharmazeutische Technologie beschäftigt sich nicht nur mit der Herstellung und Verbesserung der Herstellung der klassischen Arzneiformen, sondern sieht ein Hauptarbeitsgebiet im Drug Targeting." Von der Diskussionswürdigkeit dieser Begriffsdefinition abgesehen, sind für die Autoren Pharma-Technik und Pharmazeutische Technologie offensichtlich identisch. Bei näherer Betrachtung der Zusammenstellung der im Lexikon aufgeführten Begriffe ist allerdings festzustellen, dass das Lexikon der Pharma-Technik sicher kein Lexikon der Pharmazeutischen Technologie ist. Fachbegriffe aus den Bereichen der Herstellung und Entwicklung von Arzneiformen oder gar aus dem Gebiet des Drug-Targetings sind entweder nur sehr knapp erläutert oder fehlen zumeist ganz. Die inhaltlichen Schwerpunkte des Lexikons der Pharma-Technologie liegen vielmehr, wie es der erweiterte Titel auch präzisiert, bei Werkstoffen und Verfahren die beim Bau von pharmazeutischen Produktionsanlagen eingesetzt werden. Der Pharmazeutische Technologe kann so beim Durchblättern des Lexikons viel über austenitische Stähle, über das Schweißen, über die Oberflächenbehandlung von Stählen, bis hin zu irrtümlich angenommenen Effekten beim Schweißen (Sandwich-Effekt) erfahren. Der Anlagenbauer kann einige Begriffe der pharmazeutischen Technologie kennenlernen, über Arzneiformen und deren Herstellung erfährt er allerdings sehr wenig. Literaturhinweise zum vertiefenden Studium fehlen leider gänzlich.

Der vom Verlag erhobene Anspruch, mit dem vorliegenden Lexikon einen fundierten Zugriff auf alle praxisrelevanten Themen von der Entwicklung, der Produktion bis hin zum Vertrieb zu ermöglichen, ist sicher zu weit gefasst, um schon mit der ersten Auflage alle Wünsche zu erfüllen. So werden mit weiteren Auflagen oder eventuell auch weiteren Bänden in Zukunft bestehende Lücken sicher noch gefüllt werden, einige Eintragungen noch kritisch reflektiert werden (wie zum Beispiel „Wassermolekül") und in einigen Fällen wird der im Lexikon abgehandelte spezielle Gebrauch eines Fachbegriffes vermutlich auch noch um die allgemeine Definition erweitert werden (wie zum Beispiel „Energieniveau"). Besonders wichtig erscheint es auch, dass zukünftig Begriffe, die innerhalb der vom Lexikon der Pharma-Technologie abgedeckten Fachdisziplinen unterschiedlich verwendet werden, auch in ihren unterschiedlichen Bedeutungen dargestellt werden, wie zum Beispiel beim „Marangoni-Effekt", der nicht nur beim Schweißen sondern auch bei Arzneiformen (zum Beispiel bei Schäumen) eine wichtige Rolle spielt.

Weitschies (Greifswald)