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Calibration transfer from a laboratory NIR instrument to the NIR-Checkmaster to determine the API content of tablets

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According to Process Analytical Technology (PAT) it is important to check certain parameters during tablet production. These parameters include the tablet weight, the diameter, the thickness and the hardness. For this purpose the **Checkmaster** of the Kraemer GmbH ELEKTRONIK can be integrated into the production process.

Apart from these physical parameters the content of **active pharmaceutical ingredients (API)** plays an important role in the tableting process as well.

To combine the analysis of the physical parameters by means of the Checkmaster with the analysis of the API content, a cooperation of the companies FETTE Compacting GmbH, Kraemer GmbH ELEKTRONIK and BÜCHI Labortechnik AG led to the development of the **NIR-Checkmaster**.

This instrument integrates the measurement of the API content by means of **NIR spectroscopy**, the tablet weight, the tablet thickness and diameter as well as the tablet hardness. For the tablets undergoing the API content analysis the hardness determination has to be switched off.

The API content analysis directly after tablet production enables to react immediately to the process variations. The Figures 1 and 5 show the NIR-Checkmaster with the integrated spectrometer NIRFlex Solid Transmittance.



Fig. 1: NIR-Checkmaster with NIRFlex Solid Transmittance

Prior to a direct online API content analysis with the NIR-Checkmaster during the tableting process, a stable and robust **calibration** for the tablets under investigation has to be created on a suitable laboratory NIR instrument. For this purpose, the NIRFlex N-500 with the Solid Transmittance measuring option from BÜCHI Labortechnik AG was used.

The **NIRFlex N-500 Solid Transmittance** spectrometer system consists of the NIRFlex N-500-spectrometer and a software package. The NIRFlex N-500 is a single beam polarization interferometer. The gained interferogram is converted to a spectrum by means of a Fourier transformation. The NIRFlex N-500 Solid Transmittance operates with the simple and comfortable transmission measurement for solid dosage forms like tablets and capsules (Fig. 2). The sample plates are specifically designed for various samples of tablets and capsules. Typical sample types for the NIRFlex N-500 Solid Transmittance are tablets (with and without coating), hard gelatine capsules, powders or soft gelatine capsules containing liquids or oily liquids.



Fig. 2: NIRFlex N-500 Solid Transmittance with different sample plates

To obtain reproducible and precise results for the transmission measurement of tablets, it is important to avoid scattered light escaping from the tablet sides. Thus, for an optimal performance, the sample plates are exactly matched to the analyzed samples. A stable measuring cell and the direct drive of the sample plates ensure highly reproducible measuring results. Apart from that, the plates are provided with a special coating to avoid reflexion and an un-

wanted occurrence of scattered light. The sample plates can accommodate up to 30 samples with a diameter of 4 to a maximum of 12 mm. For larger samples with a diameter between 12 and a maximum of 30 mm sample plates for up to 10 samples are available.

Figure 3 illustrates the detector position and the light path of the NIR light. Figure 4 schematically shows the light path from the lamp to the detector, passing through a tablet.



Fig. 3: Detector position and light path

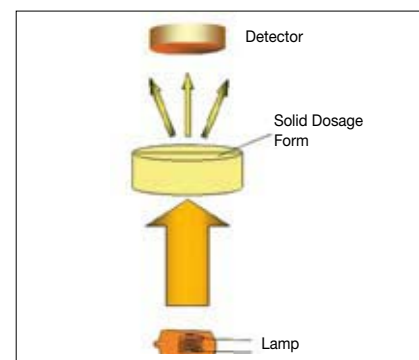


Fig. 4: Diagram of a tablet analysis

The Buchi software package for the laboratory instrument consists of the NIRWare Management, the NIRWare Operator and the chemometric software NIRCal. The software fulfils the requirements of the pharmaceutical authorities.

The NIRWare Management Console allows for an easy and fast creation of NIR applications. NIRCal is used to compute and optimise the calibrations. The measurement is carried out by means of the NIRWare Operator. Input fields for sample information and SOPs enable to respond to individual user requirements.

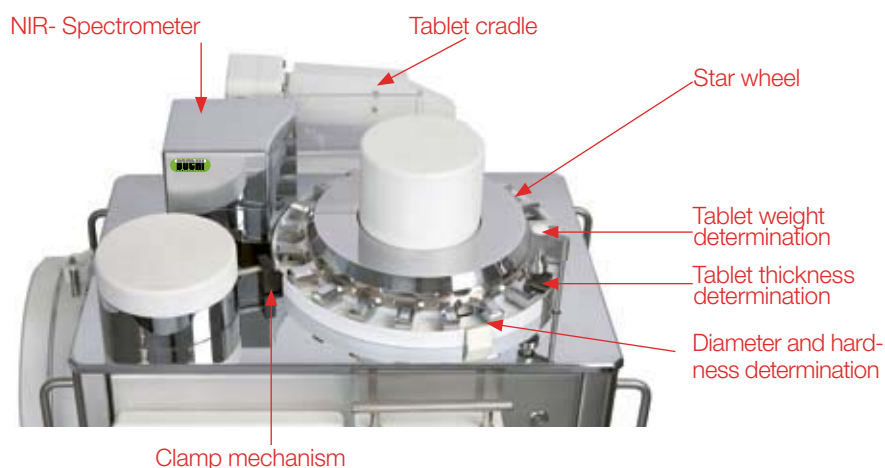


Fig. 5: NIR-Checkmaster, top view

The **NIR-Checkmaster** is not equipped with tablet sample plates. Here, the tablet samples coming from the press are fed individually into the star wheel via the tablet cradle.

While the star wheel is rotating, it passes automatically the individual positions for tablet weight, thickness, diameter and hardness measurement. When the tablet reaches the clamp mechanism of the NIR instrument, the clamps are extended and pick up the sample. Now the sample is adjusted by the two clamps holding it in two format-specific cups and transported into the NIR measuring cell. Thus, the unwanted occurrence of scattered light can be avoided and a high reproducibility of the results is achieved. After the measurement was carried out according to the same principle as on the laboratory NIR instrument, the clamps remove the sample from the measuring cell. The instrument is now ready for the next measurement.



Fig. 6: Format-specific cups with two clamps (open and closed)

Figure 6 shows the two format-specific cups with two clamps for Captopril 25mg tablet to be measured with the NIR-Checkmaster.

As the NIR-Checkmaster is provided with the same software package as the laboratory instrument, the calibration created on the laboratory instrument can be transferred to the NIR-Checkmaster without any problem.

To test whether the NIR-Checkmaster delivers the same reproducible results of the sample's API content with these transferred calibrations as the laboratory instrument, different comparative measurements were carried out. For this purpose, 60 tablets were analyzed on the NIR-Checkmaster and on the laboratory NIR instrument with the same calibration. The tablets analyzed in this case were from a routine production

and were supposed to have an API content of $25 \text{ mg} \pm 5\%$ per tablet ($23.75 - 26.25 \text{ mg}$ API content per tablet).

The results shown in Table 1 indicate that a calibration created on the laboratory instrument NIRFlex N-500 Solid Transmittance can be transferred to the NIR-Checkmaster without problems and without considerable deviations. Table 1 shows only 10 of the 60 measurements. The slight deviations of all 60 values of a minimum of 0.06 % to a maximum of 1.48 % for the determined API content are negligible.

To clearly illustrate that the slight deviations do not occur systematically, the measuring results were additionally mapped in a diagram (Fig. 7).

To make a concrete assessment of the measurement accuracy of both instruments, the determined results for the API content from the laboratory instrument and from the NIR-Checkmaster were compared to the results gained from the subsequent validated HPLC method (Table 2). Six samples were analysed and the comparison produced minimal deviation of the individual measurement results from the reference values. These deviations are comparable to the allowed standard deviation of the validated HPLC method.

Fig. 8 shows a graphical comparison of the determined API contents from the laboratory NIR instrument, the NIR-Checkmaster and the HPLC method.

Tablet	Laboratory instrument API Content [mg]	NIR-Checkmaster API Content [mg]	Deviation [%]
1	25.726	25.691	0.14
2	26.090	26.053	0.14
3	25.426	25.263	0.64
4	25.263	25.130	0.53
5	25.276	25.142	0.53
6	25.191	24.958	0.92
7	25.728	25.555	0.67
8	26.130	25.742	1.48
9	24.702	24.607	0.38
10	25.190	25.210	-0.08
Average deviation of the 10 results [%]			0.54

Table 1: Calibration transfer from the laboratory instrument to the NIR-Checkmaster

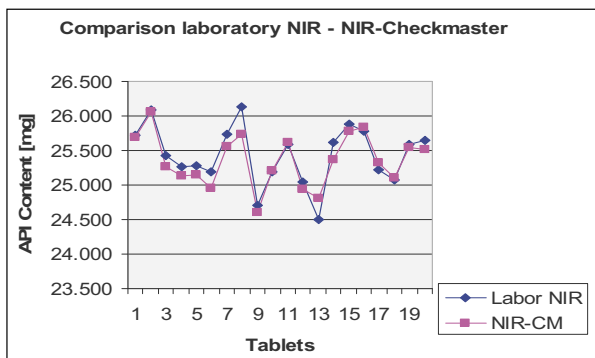


Fig. 7: Comparison lab instrument to the NIR-Checkmaster

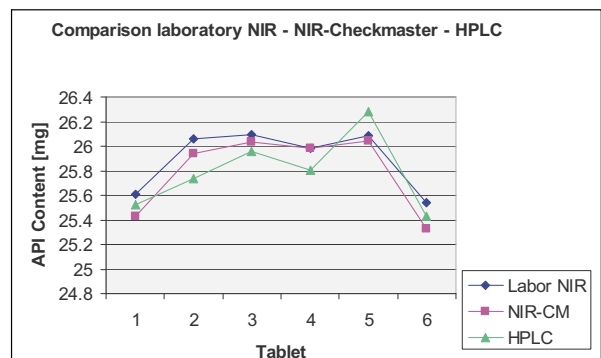


Fig. 8: Comparison lab instrument NIR-Checkmaster - HPLC

Table 2 and Fig. 8 suggest that the determination of the API content for tablets by means of the laboratory instrument or the NIR-Checkmaster can be an alternative to the time-consuming HPLC method used so far. It is clearly visible that the results obtained with the NIR-Checkmaster are even slightly closer to the results obtained with the previous validated HPLC method than the values obtained with the laboratory instrument. Therefore, considering the accuracy and the expenditure of time for the API measurement, the use of the NIR-Checkmaster is a valid alternative to the HPLC method.

Tablet	Laboratory instrument API Content [mg]	NIR-Checkmaster API Content [mg]	HPLC API Content [mg]	Deviation [%]
1	25.605	25.427	25.523	0.36
2	26.061	25.943	25.739	0.65
3	26.095	26.035	25.959	0.27
4	25.987	25.986	25.805	0.42
5	26.084	26.044	26.278	0.50
6	25.543	25.328	25.432	0.43
Average deviation of the 10 results [%]				0.44

Table 2: Comparison laboratory instrument and NIR-Checkmaster to the HPLC results

The HPLC method needs about 13 minutes without sample preparation to measure the API content of one tablet used in this case. A measurement with the NIR-Checkmaster only takes about 20 seconds. Thus, when using the NIR-Checkmaster for the determination of the API content of tablets, 40 tablets can be analyzed with the novel NIR measuring process at the same time that is needed to carry out just one HPLC analysis. This comparison does not include the time needed for the laborious sample preparation prior to an analysis with the HPLC method.

The new NIR-Checkmaster represents a key step towards an integrated PAT philosophy. Modern FT-NIR technology and high-end mechanical engineering deliver stable and reproducible results in "real-time".

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