

A PAT initiative upshot: on-line tablet content uniformity analysis using FT-NIR spectroscopy

A. Giehl,^a J.C. Richmond,^a S. Hammond^b and N. Broad^b

^a Bruker Optics Limited, Banner Lane, Coventry, CV4 9GH, United Kingdom

^b Pfizer, Ramsgate Road, Sandwich, Kent, CT13 9NJ United Kingdom

Introduction

Process Analytical Technologies (PAT) describes a new initiative leading pharmaceutical manufacture into a new era. PAT initiative allows pharmaceutical companies to benefit from new and evolutionary process technologies as has already taken place in other industries. Benefits are:

- Increased production capacity and efficiency
- Lower production and monitoring cost
- Reduction/elimination of out of specification material (OOS)

This paradigm shift i.e. moving from end of phase testing towards continuous quality testing during each phase means that cycle times can be reduced and therefore the production capacity can be increased.

Bruker Optics Limited has special expertise in the applications of FT-IR and NIR to pharmaceutical products. Applications range from incoming raw materials to testing of the final product. The Pharmaceutical Industry presents particular challenges for instrumentation, in throughput, in accuracy and, not least in terms of validation. Bruker Optics has seized the PAT initiative by introducing products specifically designed to address these issues. An example of this is the automated tablet analysis, which is important in tablet manufacture for measurement of potency and content uniformity.

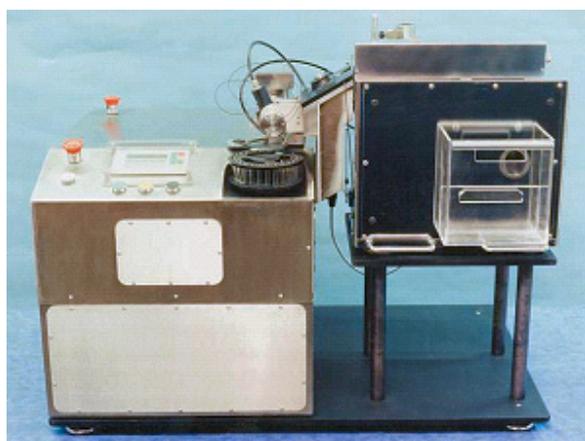


Figure 1. Tandem system comprising of a conventional tablet tester for weight, thickness, diameter and hardness and a Bruker FT-NIR spectrometer for measurements of tablets in transmission mode.

Instrumentation

In cooperation with Pfizer, Bruker has therefore developed a new system called TANDEM, which combines on-line NIR content uniformity with traditional tablet testing on weight, thickness, diameter and hardness. Tablets are automatically delivered from the press to the TANDEM, where weight and thickness is measured on each tablet. Tablets are then taken either to the diameter and hardness station, where they finally get crushed and binned, or they are taken to the NIR unit of the TANDEM, where the identity of a single tablet is maintained by loading the analysed tablet in a 25 position storage carousel.

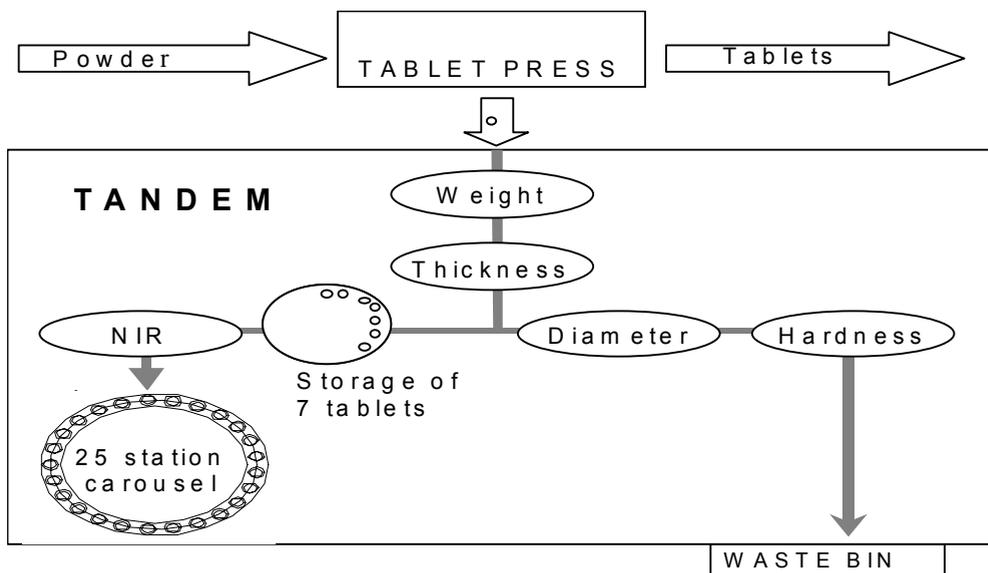


Figure 2. Flow of tablets from the press to the Tandem. Weight and thickness is analysed on all tablets delivered by the press automatically. Tablets are then either taken to the diameter and hardness measurement station or taken to NIR analysis. After NIR analysis tablets are stored in a carousel where the identity of each tablet is kept.

A Bruker Matrix-TANDEM Fourier Transform Infrared spectrometer is incorporated in the TANDEM for NIR analysis. The spectrometer comprises the Rocksolid™ interferometer and a detector head with collecting optics. The interferometer is permanently aligned with cube-corner mirrors that require no dynamic alignment. All optics are gold coated in order to provide an excellent signal to noise ratio. The interferometer is a “double pendulum” design that is very rugged and reliable. It is also insensitive to vibration or thermal shock. The unique design of the detector probe head provides a large distance between the tablet and the detector and there is no risk of cross contamination between samples.

Special care has been taken when designing the tablet nest for presenting tablets into the NIR light beam, as accurate automatic positioning of tablets is vital for the successful monitoring of the potency of the drug.



Figure 3. On-line NIR analysis of tablets. Tablets are positioned automatically into a customised tablet nest, which is then transferred underneath the NIR reading head. After completion of the NIR analysis tablets are collected in a 25 vial storage carousel.

Application

NIR feasibility study

In order to monitor the potency of a batch using FT-NIR spectroscopy, spectra are taken in transmission in the spectral range from 12000 – 7500 cm^{-1} (700 – 1500 nm). The co addition of 16 scans per spectra at a resolution of 8 cm^{-1} allows a fast measurement of less than 10 seconds per spectrum.

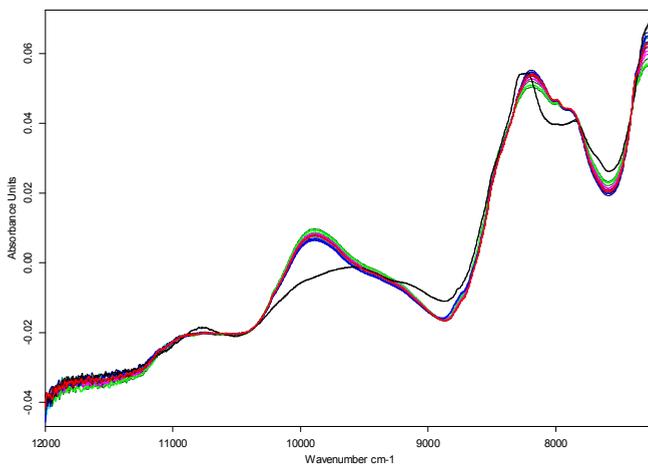


Figure 4. NIR spectra of tablets measured in transmission mode.

The increase of the concentration of an active drug is shown in the spectra allowing the build up of a calibration model with an excellent Standard Error of Cross Validation (RMSECV) of 0.015 mg/Tab and a correlation coefficient R2 of 99.95 %. The unique self-optimise function in the OPUS software was used to develop the model. The calibration range covered a concentration of 0.1 to 2 % of the active drug.

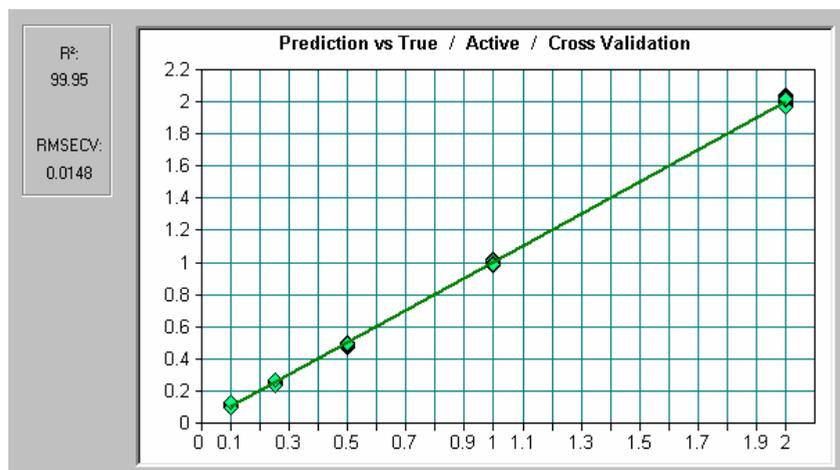


Figure 5. Calibration model for tablets measured by FT-NIR in transmission mode. The concentration range is from 0.1 to 2 % of the active drug.

On-line measurements

Within the on-line measurement set up, tablets may be analysed using qualitative or quantitative methods or both. The calculation of the mean concentration and the relative standard deviation of sequential groups of tablets (content uniformity) may be used to monitor the manufacture of tablets within specification limits.

If OOS material or outliers are detected, this is shown in real time and warnings are given to the operator, who can easily monitor on the screen the flow of the tablets through the TANDEM system. The software package for the TANDEM is fully compliant with 21 CFR Part 11 and fits the customers ERES requirements.

Conclusion

When integrating the FT-NIR technology to a tableting machine or a conventional “weight, thickness, hardness” analyser, instant determination of the potency of the tablet during manufacture is easily available. The robustness of Bruker FT-NIR spectrometers allows the installation next to the tablet press and an IP65 stainless steel enclosure protects the total system from dust during tablet compression and from water during washdown procedure. FT-NIR spectroscopy can therefore be used for optimisation of the manufacture of tablets, leading to a substantial reduction of production costs. This PAT implementation ensures “right first time” manufacturing with all batches produced in specification.

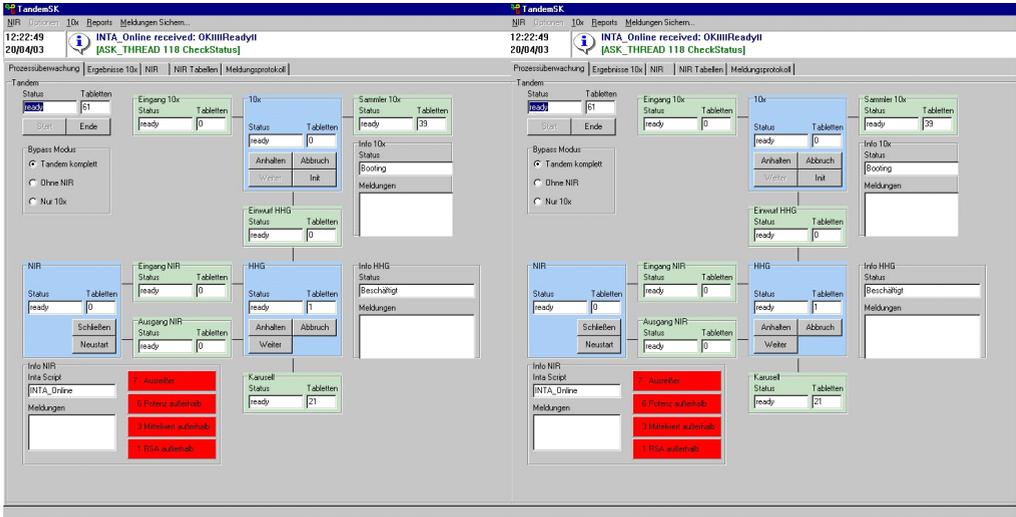


Figure 6. Online display of analysis results. The Tandem software package allows real time graphical display of NIR analysis results. Potency, average potency and %RSD are displayed in table format also. The control page will allow an overview on the flow of tablets through the Tandem system