Application Notes

TANDEM FT-NIR for on-line tablet characterisation

Pharmaceutical manufacturers are required to enhance their critical quality performances. This is being encouraged by the FDA, which is pushing towards using modern process analytical technology (PAT) to ensure the quality of the final product. A large number of applications in the Process Analytical Technology (PAT/QbD) initiative can be addressed using FT-NIR spectroscopy. For drug product sites for instance, NIR spectroscopy can be used at almost every step of tablet manufacture from raw material control over granulation and drying to content uniformity analysis of the dosage unit.

Bruker has developed the TANDEM, which is an integrated, automated, on-line pharmaceutical tablet characterisation tool providing tablet weight, thickness, diameter, hardness and NIR content uniformity analysis. TANDEM can:

- Provide tablet weight, thickness, diameter, hardness and NIR content
- Perform uniformity analysis
- Measure over 300 tablets per batch
- Full validation with IQ/OQ/PQ documentation and USP/EP protocols
- Can be connected to any tablet press via OPC communication.

Comprehensive solution

Traditionally, content uniformity analysis has been performed by HPLC. This high volume, time-consuming, labour-intensive process requires that test samples be taken from the production area to the QC/QA laboratory where they are prepared and analysed. TANDEM provides a comprehensive solution for the pharmaceutical industry, providing not only content uniformity but also a full set of tablet characterisation parameters including weight, size, thickness, hardness and diameter in a single analyser. The system consists of a Bruker MATRIX FT-NIR spectrometer, a Sotax 10X or AT4 tablet testing system and a tablet handling unit. TANDEM can be integrated with existing tablet pressing systems for automated analysis. Additionally, the analysis information can be used immediately to adjust production parameters to improve product uniformity.

Measurement sequence

Throughout a batch, multiple locations of several tablets are typically sampled for NIR analysis. The measurement sequence can be performed so that the sampling rate is intensified at the start and end of a batch, where abnormalities in tablet manufacture are more likely to happen. All tablets analysed by NIR are stored in a way that the identity of each individual tablet is retained.

Real time data

The control window of the TANDEM process software offers a precise overview of the positions of all tablets delivered from the tablet press. In addition, all results produced by the TANDEM on the current run are displayed on the screen and are available as OPC tags (including status and alarms). For NIR results, a graphical display of the potency of each tablet as well as the average and their %RSD is shown. After completion of the batch, a full report is available.

Figure 1: TANDEM is an on-line pharmaceutical tablet characterisation tool, which incorporates the Sotax 10X conventional tablet tester and Bruker's MATRIX FT-NIR spectrometer

Implementation

The TANDEM has been developed for use in a process environment next to a tablet press. The system has a robust design with a built-in FT-NIR spectrometer, which is insensitive to vibrations from the tablet press. The TANDEM comes in an IP 65 (10X only) rated stainless steel enclosure and is sealed against dust and sprayed water. The TANDEM has an open architecture for cleaning and product changeover.

Fit-for-Purpose MicroNIR Spectrometer

Miniature and cost-effective NIR spectrometers are starting to facilitate QbD adoption

There has been a lot of emphasis in recent years by the FDA towards applying Quality by Design (QbD) principles in the development and the manufacture of pharmaceutical products. Implementing QbD methodologies leads to a greater understanding of the process and the product, enabled by the use of on-line, at-line, and in-line process analytical technology (PAT) tools. Those technologies allow for systematic and scientific process control strategies and real-time process feedback, as well as perpetual knowledge building of the process understanding. The benefits are therefore higher quality products, improved product consistency, reduced product development cost, reduced manufacturing cost, and faster regulatory approvals.

Near infrared spectroscopy is one of the PAT tools that can be used at various stages of process manufacturing, from raw material verification, moisture content monitoring in drying processes, end point monitoring in blending, to active ingredient tablet assay.

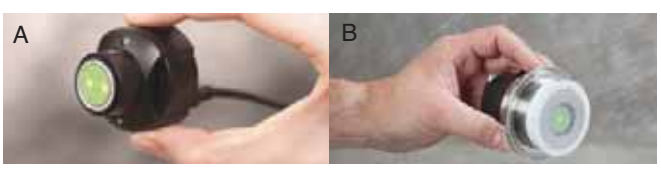

Figure 1: (A) The MicroNIR Spectrometer. (B) The MicroNIR Spectrometer enclosed in stainless steel housing suitable for PAT applications

Conventional NIR spectrometers are expensive and bulky systems designed with Czerny Turner grating-based systems or Fourier transform near infrared technology that require high precision and costly mechanical components for its operating principle. It is believed that cost-effective NIR spectrometers should assist in increasing the implementation of QbD principles. A newly-developed miniature spectrometer has broken the paradigm. Relying on the state-of-the-art in thin-film filter deposition, JDSU Corporation has developed and commercialized a miniature NIR spectrometer that weighs less than 60g and measures less than 50mm in diameter. The MicroNIR™ spectrometer is shown in **Figure 1**. The spectrometer uses a linear variable filter (LVF) component mounted over a diode array detector that separates the incoming light into the individual wavelengths. The working principle of the LVF is provided in **Figure 2**. The spectrometer integrates the light source and readout electronics inside the small construction shown in **Figure 1**. The MicroNIR spectrometer can be mounted directly on the window of a blender or a fluid bed dryer, or any other process without the need for costly fibre optic probes.

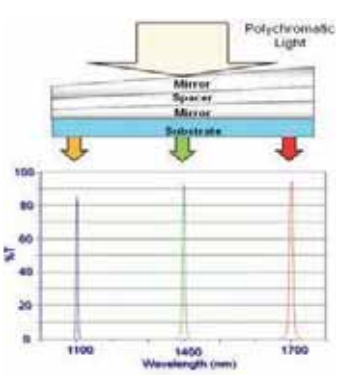

Figure 2: Working principle of a linear variable filter (NIR) component. The wedge in the thickness is applied to all layers comprising the bandpass filter design

We report here on one application example where the MicroNIR spectrometer was evaluated as part of a larger study related to NIR calibration life-cycle management, conducted at Duquesne University, Center for Pharmaceutical Technology, in Pittsburgh, Pennsylvania, USA.

At-line non-destructive API tablet assay

Tablets made of acetaminophen, lactose, microcrystalline cellulose, hydroxy propyl cellulose and magnesium stearate were created at laboratory and pilot scales. A total of 165 samples were available for calibration, 100 for test, and 60 for validation, for the development of a calibration model for the acetaminophen content of tablets using the MicroNIR spectrometer. The data had seasonal variability (high and low humidity), batch variability (different granulations), and manufacturing variability (lab and pilot scales). The active content of each tablet was measured by HPLC and an average standard error of 0.83% was determined for all tests.

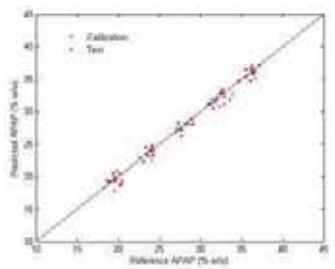

Figure 3: PLS results of calibration and test of acetaminophen content in tablets prepared and tested under controlled laboratory conditions

In controlled laboratory conditions, 45 calibration and 35 test tablets produced with the same granulation and with limited environmental changes, the RMSEP value using the MicroNIR spectrometer was 0.87%, w/w. The results are shown in **Figure 3**.

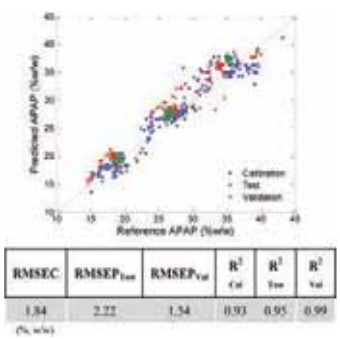

Figure 4: PLS results of calibration, test, and validation of acetaminophen content in tablets prepared and tested under variable environmental conditions. The difference in statistics between calibration, test and validation can be explained by the difference in variability included in each set.

In the presence of significant environmental variability described earlier, which is more characteristic of typical manufacturing conditions, the RMSEP was 1.54%, w/w as shown in **Figure 4**.

The results show great promise towards the successful implementation of affordable NIR spectrometers as fast and non-destructive analytical tools for tablet analysis that are essential for making timely business-critical decisions.

The MicroNIR spectrometer can be designed to operate in a wireless configuration allowing use on rotating blenders for end-point monitoring. Not only is the MicroNIR spectrometer useful as an at-line and on-line tool for monitoring batch manufacturing processes, it will be an essential on-line tool in the new and emerging continuous manufacturing processes that require continuous monitoring and real-time process control.

Optimising continuous wet granulation

Predicting tablet attributes from measurements of wet granule properties

By Jamie Clayton, Operations Manager, Freeman Technology

Wet granulation is routinely used in pharmaceutical manufacturing to convert fine and challenging powder blends into homogeneous granules that are then dried, milled and lubricated, before being fed through the tablet press, hopefully to form tablets of the desired properties. The aim therefore is to generate granules that flow consistently and, more importantly, produce high quality tablets. Whilst the granules are not the end product, it is known that their properties have a significant effect on the attributes of the tablet.

Freeman Technology and GEA Pharma Systems have conducted a study to investigate the feasibility of predicting critical quality attributes (CQA) of tablets from intermediate granule properties. This research has revealed a robust correlation between tablet hardness and the Basic Flowability Energy (BFE – a dynamic powder property) of the granules used to produce the tablet. The work demonstrates how BFE measurements have considerable potential to develop and optimise wet granulation processes and enhance product development and process control.

Experiments were performed to investigate the effect of granulator screw speed, powder feed rate and liquid feed rate, on the properties of granules produced using a ConsiGma 1™ (GEA Pharma Systems), a patented continuous high shear granulator and small batch dryer. Batches of granules produced under different operating conditions were dried, milled and then blended with a lubricant, before being fed through the tablet press.

The BFE of each batch was measured after every process step using an FT4 Powder Rheometer® (Freeman Technology). BFE values are generated by measuring the torque and force acting on a precision blade as it travels through a sample of the powder (or granules) along a defined path and directly quantifies the resistance of the sample to forced flow conditions.

The results (**Table 1**) illustrate how granules with similar properties (conditions 1 and 2 and conditions 3 and 4) can be produced by applying different operating conditions. Furthermore, they demonstrate how screw speed, powder feed rate and liquid feed rate can be adjusted to target a specific BFE. This gives process engineers the scope to employ the most appropriate production methods to target the required granule property.

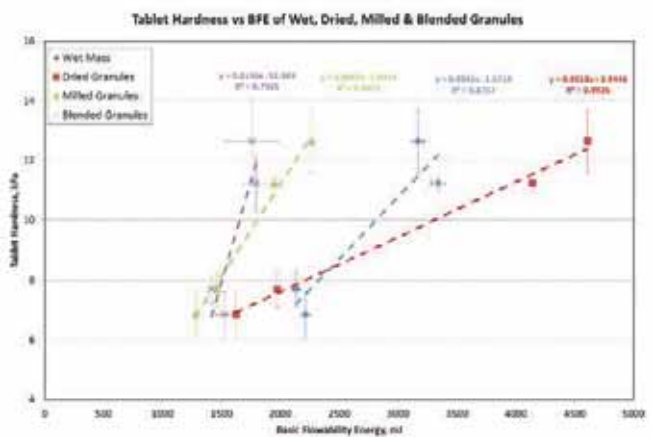

Figure 1: Direct correlations between the BFE of granules and tablet hardness demonstrate the value of dynamic powder testing in wet granulation studies

However, the ultimate objective is to be able to manipulate process parameters to ensure tablets of a certain quality are achieved.

To evaluate the feasibility of this approach, tablets were produced from each batch of granules and tablet hardness was measured using an 8M Tablet Hardness Tester (Pharmatron). **Figure 1** shows that there is strong correlation between tablet hardness and BFE values at various stages of the granulation process. This demonstrates how the BFE of the granules can be tracked to achieve a particular CQA of the final tablet. Furthermore, the model is independent of equipment type and process settings so when a target BFE is attained, tablet quality is assured. Implementing such measurement techniques simplifies product and process development, allows robust specification of the Design Space and ensures enhanced process control.

Table 1 Experimental results show how granules with similar properties can be produced using different wet granulation conditions

	Process Parameters				Granule Properties			
Condition	Screw Speed (rpm)	Powder Feed Rate (kg/hr)	Liquid Feed Rate (g/min)	Moisture (%)	BFE – Wet Mass (mJ)	BFE – Dry Granules (mJ)	BFE – Milled Granules (mJ)	BFE – Lubricated Granules (mJ)
1	450	11.25	15.0	8.0	2217	1623	1283	1526
2	750	20.0	36.7	11.0	2133	1973	1463	1417
3	450	6.0	20.0	20.0	3172	4610	2268	1761
4	750	9.0	30.0	20.0	3342	4140	1951	1795

Investigating the lipolysis of lipid nanoparticles: impact on drug release properties

Solid Lipid Nanoparticles (SLN) and Nanostructured Lipid Carriers (NLC) are colloidal systems of interest for the delivery of poorly water-soluble drugs. They are fine lipidic emulsions with droplet size of about 50 – 1000 nm, in which the liquid lipid of a regular emulsion is replaced by a solid core[1]. The core is composed of triglycerides, glyceride mixtures or waxes that are solid at both room and human body temperature. Triacylglycerols (TAGs), diacylglycerols (DAGs), monoacylglycerols (MAGs), phospholipids, polysorbates, and polyethylene-glycols (PEGs) mono- and diesters are commonly used. All these molecules contain ester bonds that can be cleaved by lipolytic enzymes[2] present in digestive fluid. Gattefossé routinely investigates the impact of lipid excipient digestion (lipolysis) on drug behavior in lipid based self-emulsifying formulations, and has now applied the technique to investigate the digestibility of SLN and NLC.

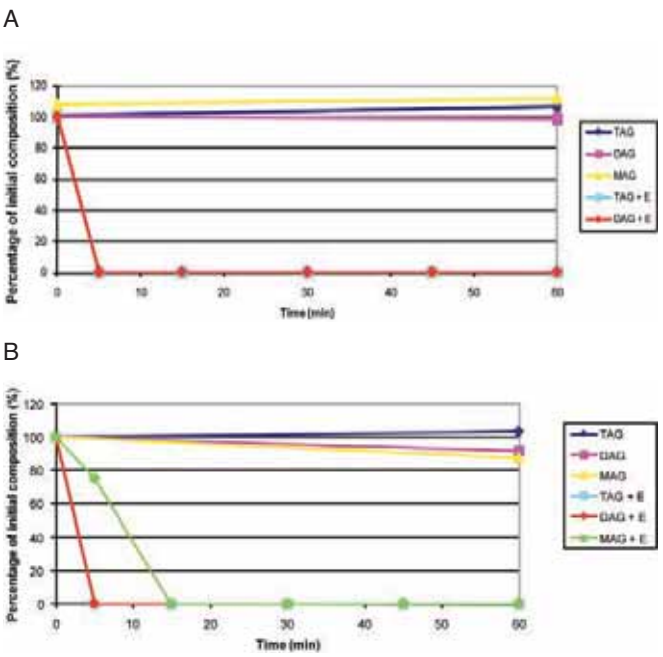

Figure 1: Composition of Precirol® ATO 5 in SLN **(A)** and NLC **(B)** during *in vitro* lipolysis at pH 5.5. E = experiments performed with enzymes.

SLN and NLC were prepared by high shear homogenisation and ultrasonication technique. Both comprise an aqueous phase of polysorbates (Tween® 80) and poloxamers 407 (Pluronic® F127). Precirol® ATO 5 is the lipidic phase of the SLN. The NLC contained Precirol® ATO 5 and medium chain triglycerides (Labrafac™ Lipophile WL 1349). Mean particle size diameter of the SLNs and NLCs was between 150 and 200 nm.

The lipolysis assay was performed using a pH stat apparatus (Metrohm® AG, Switzerland) with digestion buffers mimicking the typical concentrations in the small intestine[3]. The pH of the lipolysis medium was adjusted to simulate fasted or fed conditions. A porcine pancreatic enzyme suspension was added to start the digestion. Acetonitrile was used as the lipase inhibitor to halt digestion. SLN or NLC were added to the lipolysis buffer and pancreatic enzyme added. Sodium hydroxide was automatically added to maintain a constant pH during digestion. The periodic sampling of aliquots, followed by the addition of acetonitrile to stop the digestion process and subsequent analysis by gas chromatography, enables the degradation of the nanoparticples by lipolytic enzymes to be evaluated.

The degradation of SLN in fasted conditions (pH 5.5) was completed in less than five minutes (**Figure 1A**). MAGs were undetectable, even at t=0 possibly due to their micellization in the buffer preventing their extraction by the organic phase. For NLC, TAGs and DAGs digestion is very similar to that in SLN. The digestion of MAGs (assayed by GC-FiD) is approximately 22 per cent of in the first five minutes and 100 per cent after 10 additional minutes (**Figure 1B**).

SLN and NLC systems obtained with long-chain saturated glycerides appear to be rapidly and completely digested by pancreatic enzymes. The pH-stat lipolysis method is a straightforward tool to evaluate the digestibility of these lipid-based nanoparticles and the potential impact on drug release from these systems.

References

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2. Bakala N'Goma et al. Ther. Deliv. (2012) 3, 105-124
3. Carrière,F., et al. Gastroenterology. (1993).105, 876-888

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Having PAT NIR solutions ready for continuous processes

SentroPAT FO and SentroProbe DR LS

SentroPAT FO and SentroProbe DR LS

In recent years, the pharmaceutical industry has invested significant time, money and effort into the development and establishment of continuous processing for solid dose pharmaceuticals. At the same time, strong efforts have been made in the industry into developing the PAT tools that are mandatory for such continuous processes.

For any PAT tool deployed in a continuous process train, two major aspects have to be addressed for effective inline or online measurement. Firstly, the challenging product presentation of moving powder sample streams must be considered and is of prime importance. Secondly the level of analyser reliability and up time with the lowest need for manual intervention with the system is also a key consideration for successful implementation of PAT in this area.

The SentroPAT FO and SentroProbe DR LS systems from Sentronic cover both aspects in many unique ways and are an excellent fit to a continuous process as for example continuous granulation, blending or drying. The core component of each SentroPAT FO is a diode array based spectrometer module covering the NIR range from 1100 to 2200nm. The main advantage of this technology is the synchronous acquisition of the entire NIR spectral range within milliseconds. Due to the fact that a change or disturbance in the sample presentations affects the entire spectrum they can be identified and rejected providing the lowest feasible noise in the information gathered on the process. A further feature of the system is the capability to measure up to four different measurement ports sequentially within seconds providing multiple information in real-time in a cost effective manner using a single analyser.

Intensive development work was done on the analyser stability and reliability addressing the second important aspect of deploying PAT in continuous processing. Several internal monitoring features have been implemented into SentroProbe DR LS and SentroPAT FO. To maintain long term stability and high spectral data quality an internal intensity standard is implemented in the SentroProbe DR LS. This spectral standard is located just behind the Sapphire window which forms the sample interface allowing an automatic correction of any intensity drift within the system during a running measurement. Long term wavelength accuracy of the system is maintained by an internal calibration filter which is implemented into all SentroPAT FO units providing a defined etalon spectrum, which is not subject to a change over time.

Another important aspect to be considered is the seamless and robust integration of the analyser into the manufacturing processing and data management system. For this very generic requirement, SentroPAT FO incorporates an Embedded PC that makes the system fully self-sustaining. Using its LAN interface OPC or TCP/IP communication is possible as well as direct interfacing to data management software.

Within the last few years, the SentroPAT FO systems have been installed in a number of continuous and batch processing lines for R&D and routine operation in production of solid pharmaceutical products. The systems are used for inline measurement of potency and blend uniformity for example. Due to the high measurement speed direct rejection of out of spec material was implemented in some cases.

Sentronic was established in 1993 and with more than 20 years' experience, we are a partner for process spectroscopy to many industries. With a strong focus on PAT for solid dose products for last 10 years, we provide dedicated technical solutions to the pharmaceutical industry as well as comprehensive services and support for all our customers.

96- and 384-channel electronic pipettes

An affordable way to increase pipetting productivity

A new genre of 96- and 384-channel benchtop electronic pipetting systems has become globally popular as the demand for higher sample throughput in laboratories has increased. These benchtop systems fill the gap between standard handheld pipettes and fully automated liquid handling robots in terms of ease of use, productivity and affordability.

These 96- or 384-channel pipettes are invaluable for applications in which all channels are used simultaneously, such as starting 384 enzymatic reactions in parallel, transferring samples from one plate to another, distribution of buffers or cells from reservoirs into microplates or reformatting 96-well plates into a 384-well format or vice versa. Some 96-/384-channel pipettes also allow partial loading of individual columns and rows of the pipetting heads. This is a nice add-on, especially when you need to perform serial dilutions, so make sure the device comes with a solution to index a plate for rows or columns so you can perform dilutions in a portrait or landscape way.

The advantages of electronic versus manual pipettes with regards to user friendly ergonomics and reproducibility of the pipetting results are widely acknowledged. But some electronic 96-/384-channel pipettes offer a set of further features which manual versions cannot provide, such as support functionalities like automatic mixing of serial dilutions, repeat dispense for aliquot dispensing into multiple plates or controlled dispensing speeds for viscous liquid. The INTEGRA VIAFLO 96/384 goes even further by allowing you to automate more elaborate protocols, like for example the serial dilution of an entire well plate. These protocols can be saved on the unit and recalled anytime.

Make sure your pipette is not limited to a single volume range. What might be good for handling media in cell cultures or when washing cells with buffer is not optimal for setting up a PCR reaction and running other biochemical assays. The INTEGRA VIAFLO 96/384 allows you to easily exchange the pipetting heads on the same instrument, a choice of different working volume ranges allow you to pipette from 0.5 – 1250 µl with optimal accuracy and precision.

Today, your lab might still be working in 96-well formats, but tomorrow, you might want to switch to 384-well plates. If you see a need to work with 384-well plates down the road, it might be better to buy a pipette which can work with both 96- and 384-channel pipetting heads. If you worry about the higher cost for such a device, at least make sure your 96-channel pipette has a convenient indexing functionality for 384-well plates and provides a way to work precisely with volumes between 0.5 to 50 µl.

A 96-/384-channel electronic pipette should be as easy to use as standard handheld manual pipettes. It should allow you to intuitively control the device by hand-eye coordination and not require any prior programming or special skills of the user. The INTEGRA VIAFLO 96/384 takes this concept a step further, as all movements of the pipette are assisted by servo motors, which results in a completely effortless and ergonomic workflow.

Figure 1: Pipetting in a laminar flow hood

The modern generation of 96- and 384-channel electronic handheld pipettes have a much smaller footprint than most commercial automated liquid handling systems. Using 96-/384-channel electronic pipettes frees up valuable space on your workbench and enables them also to easily fit and be used in a laminar flow hood (**Figure 1**).

96- and 384-channel handheld electronic pipettes are a truly cost effective way to increase sample throughput and reduce manual labour without the need to invest into complex laboratory automation. Beneficially, 96-/384-channel handheld electronic pipettes lower running costs as they do not require extensive training of personnel or involve any expensive maintenance contracts. Electronic 96-/384-channel pipettes can also calibrated using a photometric procedure, a method that can be carried out in most labs.