1|2012

INNOVATIV

Topping-out ceremony
in Sassenberg

Inline Raman measurements

New fluid bed system

BÖHLE

Dear readers,

"If you don't go forward, you go backward" said the former Veba CEO Rudolf Bennigsen-Foerder. Today, this general statement is ever more significant to all manufacturers of investment goods. With fierce competition for the best products and processes, this is no time to sit back and relax.

This year we will reach the maximum construction limit for our new commercial property in Sassenberg. The expansion will allow for the production of machines worth up to EUR 50 million per year over the next two years.

In order to have sufficient capacity in 2014, however, we are currently buying around 20,000 m² of developed land from the city of Ennigerloh. We have already drafted the main features of a potential facility. Our challenge is to further improve our performance for you. Our objective, while ambitious, is to reduce the production time by one-third. A faster supply will be of great benefit to you!

At the same time, there are new requirements coming into effect in 2014 for exports by sea freight or air freight, with which we will meticulously comply. The statutory provisions require that we pack our machines in a specific zone, to which only authorized people have access. Once packed, the systems must be locked in a closed-off area until collected by the forwarding agent. These requirements will incur additional costs. In order to avoid price increases for you, we are examining all stages of the production process to reduce costs to the best possible extent.

Please note that we will undertake all efforts to be a reliable and innovative partner for our customers, even in the medium term.

Yours sincerely,
Lorenz Bohle

Going informal with the youth

Bohle at Trade Show 2011

Industry in North Westphalia is gaining pace with L.B. Bohle definitely at the forefront. At the Ennigerloh trade show on June 18th and 19th, Bohle shared a stand with five other companies. The stand underscored the "Industry Together. F|you|ture. Life." claim. This was a campaign arranged by IHK North Westphalia aiming at highlighting the critical role of industry. Successful companies go, as it were, informal with primarily the youth. The performances of the industry should be brought back into public focus and seen by others. The campaign seeks to promote trust and acceptance in this industry. "We would like to demonstrate that industrial companies are an integral part of the society," explained Lorenz Bohle. Therefore, the local enterprises are strongly involved to convey this message to the public.

Representative of the Ennigerloh industrial companies at a trade show

Topping-out ceremony in Sassenberg

A topping-out ceremony was held in plant II of L.B. Bohle Maschinen + Verfahren GmbH in Sassenberg on June 21st. This building is set to offer premises for engineers who will be relocating to Sassenberg with the entire handling development and production.

On June 27th, only a week later, District Administrator Dr. Olaf Gericke presented Lorenz Bohle a building permission to extend the company's production at the Sassenberg site. With this permission the space for the production of handling equipment can be more than doubled.

The District Administrator visited Bohle's exhibition stand at Interpack in Düsseldorf this year. During the visit, Lorenz Bohle shared his plans for extending the production premises in Sassenberg. At that time Dr. Gericke promised to personally support the granting of a permission in the near future. To Lorenz Bohle's delight, he kept his promise and handed Mr. Bohle the documents in person at the end of June.

The plan is to complete both buildings in 2011. Extension of the Sassenberg site is an urgent need for reasons of development, primarily being that there is an increasing space shortage in the production department. As a result, some components have to be stored in containers outside the building. "The new building will help ease the situation and meet our planned targets for next year's production growth," said Lorenz Bohle.

(from left to right) Architect Richard Pawlowski, Lorenz Bohle and master carpenter Georg Aufderheide at the topping-out ceremony in Sassenberg

Oktoberfest: celebrating the opening of the company's expanded production plant

The official opening of the new production hall in Sassenberg in October was celebrated with a big party.

Guests enjoyed delicacies and everything else they know from the traditional Oktoberfest in Munich, including Bavarian veal sausage, suckling pig, dirndl, a brass band, tree-trunk sawing and of course delicious beer.

The new hall will be used for the production of handling machines. The new building allows doubling of the previous capacity of the Sassenberg plant, enabling us to enhance production for our customers.

Schoolchildren show their skills

Ennigerloh, July 2011. Special works of art decorated the service center at Westkirchener Strasse from mid July to end of August.

The uniqueness of this new exhibition is its artists: a group of ninth-grade schoolchildren at Anne Frank School in Ennigerloh taking elective classes. The young creators of the secondary school shared their imaginations of machines and modern life through pictures and sculptures entitled "Engineering meets art". Lorenz Bohle expressed sincere delight when opening the exhibition. "I am amazed. I did have some expectations, but I didn't anticipate this kind of variety. Art is likely to stimulate your thinking, and the schoolchildren were able to do that with their works."

Visitors had a chance to admire the impressive art objects on the premises of the service center during the summer weeks. The exhibition will fill the summer breaks with life, with no additional pieces presented by the members of the Beckum-Warendorf Art Association.

Five employees honored

Lorenz Bohle praises commitment to raising qualification

Ennigerloh, August 2011. During a ceremony, L.B. Bohle Maschinen + Verfahren GmbH honored five employees who successfully passed their exams.

CEO Lorenz Bohle congratulated Dirk Brandt from Westkirchen on having passed the exam for Master of Electrical Engineering. The head of the company congratulated Alexander Schwarz, Michael Jasper, Holger Kirchhoff and Rafael Block on their degree in Engineering. "It is just great that my employees are also socially active in the community, seek a higher education after years of being out of school, and are now able to reap their well-deserved rewards," said Lorenz Bohle at the ceremony. "We are very delighted to have such highly qualified specialists among us."

Lorenz Bohle together with the successful graduates and Armin Bohle

Over 170 years of experience

Employees with a long work record distinguished

Ennigerloh, August 2011. Another occasion for celebration: the anniversaries of several employees who have been working more than 10 or even 25 years at L.B. Bohle Maschinen + Verfahren GmbH. CEO Lorenz Bohle handed anniversary certificates of the Chamber of Industry and Commerce to four of his employees who had faithfully stood by the company from the very beginning. Carsten Keller, Head of Process Engineering, Hubert Fartmann of the Technical Internal Sales Department, industrial mechanic Klaus De Bock and machine engineer Marius Höner were honored for their commendable work. "I am very proud to be able to reward such valuable and experienced employees," said Lorenz Bohle when handing out the certificates.

Irena Bender, Ulrich Hanskötter, Ursula Hermann, Martin Knapp, Enrico Knaup, Matthias Strate and Oliver Wagemann celebrated their ten-year anniversary in the company.

Lorenz Bohle together with the employees who have been working more than 25 years at L.B. Bohle and Armin Bohle

An employee with a long work record "flies out"

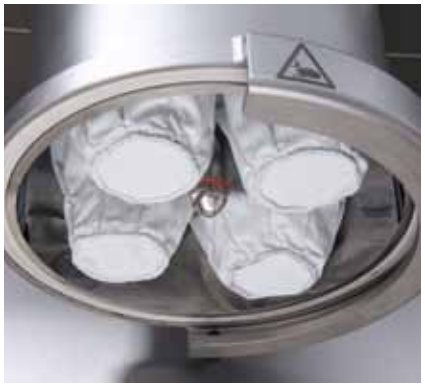
Nobert Keitlinghaus, operations supervisor, leaves the company after twelve years with Bohle. However, his spectacular "fly-out" was voluntary. On his last working day, his colleagues arranged for a helicopter to take the master of metalwork home, as would be appropriate. Norbert Keitlinghaus will continue to work as a supplier for Bohle and provide the company with assemblies in the future. "We'd like to thank Norbert Keilinghaus for his tremendous work at Bohle and look forward to establishing a productive and long-term relationship with his company," said Lorenz Bohle in bidding farewell to his loyal employee.

Norbert Keitlinghaus (right) just before the start

Bohle presents its new fluid bed system

BFS 3 presented

Bohle's fluid bed series has been extended with lab system BFS 3, the most compact fluid bed version. This system can dry up to three kilograms of granules. The BFS 3 can certainly be used for layering and pellet coating as well. The system has four filters installed and can be easily cleaned. As usual with systems of other sizes, the entire filter surface in the lab system can be easily cleaned at regular intervals by using compressed air. Furthermore, this most compact design of the fluid bed system can be equipped with an online humidity measurement unit for drying. This means of control allows repeated precise measuring of current humidity during the entire granulation and drying process.



A continuous coater consumes less suspension and improves quality

Ennigerloh, September 2011. Continuous coating processes have been nearing their limits due to stringent quality requirements in the pharmaceutical industry. Consequently, Bohle's engineers have developed a semi-continuous coater made of the company's proven coating components. The process was optimized by using modified drums, more nozzles and increased drying air.

This allows quick and high-quality reproduction of all coating applications using the Bohle KOCO®. In addition, the coater is filled and discharged automatically resulting in uninterrupted operation and with no manual intervention required by the user, i.e. continuously.

The advantages of KOCO® include easy handling and high quality of tablet coating. "In terms of engineering, we definitely stand head and shoulders above the rest," explained CEO Lorenz Bohle. The system features both shortest cycle times and extremely even suspension coating. This results in "a tolerance of below three percent". This high accuracy is particularly decisive for tablets where the suspension film either contains a substance or where there is a time-limited release of the protection cover for the substance. At the same time, the innovative nozzle arrangement significantly reduces spray loss as well as suspension application. "With a spray loss of less than five percent we are able to reduce the other values to a third," said Lorenz Bohle. In view of high raw material costs, this advantage yields substantial savings in a short time. These developments are accounted for by a new air supply unit as a powerful spraying system.

The objective: a market share of more than 30 percent

Continuous batch production with automatic filling and discharge helps further reduce the costs and time. Besides, after each sub-batch the system always discharges the contents completely. PAT tools can be integrated as an option. Last but not least, Bohle's KOCO® can be cleaned easily and efficiently, just as the customers of batch coaters are accustomed to seeing.

With its new generation of coaters, the company sees considerable growth potential in the coming years. "The global market has been heavily fragmented. Bohle holds about five percent," noted Lorenz Bohle. "Our objective in the next five years is to achieve a market share of 30 to 35 percent in this segment."

The suspended coater

During the summer, Bohle's engineers delivered a coater at a record-breaking pace. Our specialists were able not only to convince through early commissioning, but also provide an excellent solution to a challenging installation. A Bohle BFC 600 film coater was supplied to the Salutas Pharma GmbH in Barleben to be installed on the second floor of the production facility. For this purpose, our employees "packed" the BFC 600 into a frame that was specially manufactured for the building's architecture in order to transport the coater. The standard handling equipment was altered and equipped with rolls. "That allowed us to glide in the five-ton system more easily and move it inside", said construction manager Robert Stauvermann.
In addition, a Bohle engineer supported by the Salutas team and a local transport company delivered the machine on Saturday, as the outer facade of the building had to be opened for installation. The excellent preparation work allowed for a smooth installation. "It took us about six hours to put the machine in place in the production facility", reported the construction manager.

This exemplary workflow characterized the entire project. The project's ambitious goal was to hand over the plant on September 1st 2011. Therefore, the project management of Salutas and Bohle decided to commission the plant on the customer's premises. The delivery was made in two parts. The technical equipment was supplied and mounted already in May. The delivery and assembly of the said coater occurred on June 25th. The new plant was first tested in early August: "The initial results revealed the parameters stipulated in the specific requirements of a 25% reduction in process time were complied with and that the potential can be increased through further optimization processes", sums up the now satisfied project manager Marco Schroeder.

Reduction of process time by 25 %

Interview with Marco Schröder and Fred Wulfgramm of Salutas Pharma GmbH

Since 1996, Salutas has been producing generic drugs at the Barleben and Osterweddingen sites near Magdeburg. In 1996, Bohle delivered basic systems for the installation of the first production line. With its expansion in summer 2011, the pharmaceutical manufacturer relied again on Bohle quality. Innovativ interviewed Marco Schröder (Operating engineer for production technology) and Fred Wulfgramm (Head Engineering Barleben and Osterweddingen):

Your company already uses Bohle systems. Which ones have you been using and for how long?

Fred Wulfgramm: At our Osterweddingen and Barleben sites we currently have six granulators (VMA 20 to VMA 1200), two container mixers (PM 600, PM 2500), various lifting columns, sieve systems, containers and, most recently, a BFC 600 coater in operation. The oldest system dates back to 1996, and the latest was commissioned at the end of August 2011.

What are your experiences with these machines and systems?

Marco Schröder: The results have been very positive. The systems operate reliably and are trouble-free – apart from usual (inevitable) minor technical problems. One of the reasons is the joint continuous further development of the equipment by taking internal improvement suggestions into account.

You have just decided in favour of a Bohle Coater. Which essential features have you specified for the new system in advance?

Marco Schröder: For the production it is of paramount importance to process coater batches in sizes from 300 kg to 700 kg. A further requirement is that the change between the products could be implemented without extensive setup. The new coater is aimed to reduce process times and designed to a seven-day/three-shift production.

Fred Wulfgramm: Another essential aspect was the short/fast delivery capability of the machine manufacturer from placing the order until complete hand-over to production. Moreover, our focus was on ergonomic filling and discharge, an excellent GMP design including documentation and ATEX-compatible assessment.

What were the deciding factors for choosing a Bohle BFC?

Fred Wulfgramm: We contacted several potential suppliers in advance and discussed possible solutions with regard to optimizing our coating processes. During these preliminary talks, Bohle's innovative coater technology and process control convinced us.

Marco Schröder: Moreover, Bohle offered us the option to run tests on a BFC 400 at another customer's facility. Following this test and assessment of the results, as well as on the basis of an assessment matrix, our company together with the production, procurement and technology department opted in favour of Bohle.

Which production targets have you set for the coater? Can you assess how much process time is saved when using this system or whether there are any other areas were savings can be achieved?

Fred Wulfgramm: The aim is that the new coater should optimize existing coating

(from left to right) Marco Schröder and Fred Wulfgramm of Salutas Pharma GmbH

processes as well as a reduce the batch time. To this end, we agreed on a reduction of the batch process time by 25 % vs. the previous coater.

How were your first experiences with the system? Can you describe them?

Marco Schröder: The initial results revealed that the parameters stipulated in the specific requirement of a 25% reduction in batch time were complied with and that the potential could be increased through further optimization processes. Furthermore, we had fewer suspension losses which, however, they cannot be measured at present.

Fred Wulfgramm: Currently, we are focusing on the optimization of cleaning processes. However, we anticipate that the optimization potential can be significantly increased after completing the project.

Inline Raman measurements as a PAT method for coating processes in a drum coater

Institute of Pharmaceutics and Biopharmaceutics, Heinrich-Heine University, Düsseldorf

Introduction

Tablet coating is a frequent basic operation in the production of solid dosage forms. Tablets are coated for various reasons (see the table). Coatings with active ingredients are particularly critical for quality requirements. It must be ensured that during the coating process a precisely defined amount of a substance is applied evenly onto each tablet. Therefore, procedures for identifying the end of the coating process as accurately as possible are necessary. The "process analytical technology" (PAT) is a system that consists of methods for analyzing, understanding and controlling a process [1]. In addition, important tools are used to implement quantitative inline measurement methods often combined with multivariate data analysis. Raman spectroscopy is a special procedure for monitoring the coating process in a drum coater. The first results were published by Romero-Torres [2] and El-Hagrasy [3]. The objective of these tests was to establish and validate Raman spectroscopy, in combination with multivariate data analysis, as a PAT method in coating substances in the drum coater, as well as to employ it as a means of control.

Reasons for tablet coating:

- Protection from light, oxygen and/or humidity
- Improved compliance (coloring)
- Improved appearance and ease of swallowing
- Taste masking
- Resistance to gastric juice
- Delayed release of the substance
- Application of an (additional) substance

Material and methods

Drum coater: lab-scale tests were conducted in a BFC 5 lab coater (L.B. Bohle, Ennigerloh, Germany) under a load of 3.5 kg of tablet cores (see process conditions [4,5]). Scale-up tests were conducted in a BFC 50 TriPan (L.B. Bohle) under 30 kg (see process conditions [5]).

Raman equipment: we used a Raman spectrometer with a monochromatic laser source (785 nm) and a PhAT probe (Kaiser Optical Systems, Ann Arbor, USA). The PhAT probe allows contactless measurement at a distance of 15 to 25 cm and a material-dependent penetration depth of about 2 mm, the laser spot diameter being 6 mm. Figures 1 and 2 show PhAT probes integrated in the BFC 5 or BFC 50.

Reference method: UV spectroscopy served as a reference method for the quantitative calculation of diprophylline content (lambda 2, Perkin Elmer, Überlingen, Germany) at a wave length of 273 nm.

Material: the placebo tablets (7 mm diameter, biconvex) consist of lactose monohydrate (Tablettose® 80), microcrystalline cellulose (Avicel® PH 101) and magnesium stearate. The coating formula contains hydroxypropylmethylcellulose (HPMC, Walocel® HM5 PA 2910), Macrogol 1500, water and diprophylline as model pharmaceutical substance.

Validation

Validation is needed to perform analysis for process control and/or batch release. The ICH guideline Q2 [6] sets criteria to be considered during validation. Raman spectroscopy was validated based on the criteria of specificity, accuracy, linearity, detection and determination limit, precision and scope by using a validated UV reference method [7]. A concentration-dependent change in the Raman signal serves as a basis for the quantitative calculation of any substance (diprophylline in this case) by using Raman spectroscopy. Figure 3 shows Raman spectra in a wave number range of 1,200 to 1,400 cm^{-1} of tablets with varied content of diprophylline in the coating, i.e. the change in spectra during coating. In particular, significant spectrum changes can be seen in the range of 1,290 to 1,330 cm^{-1}.

Raman data used for validation were retrieved offline for coated tablets with var-

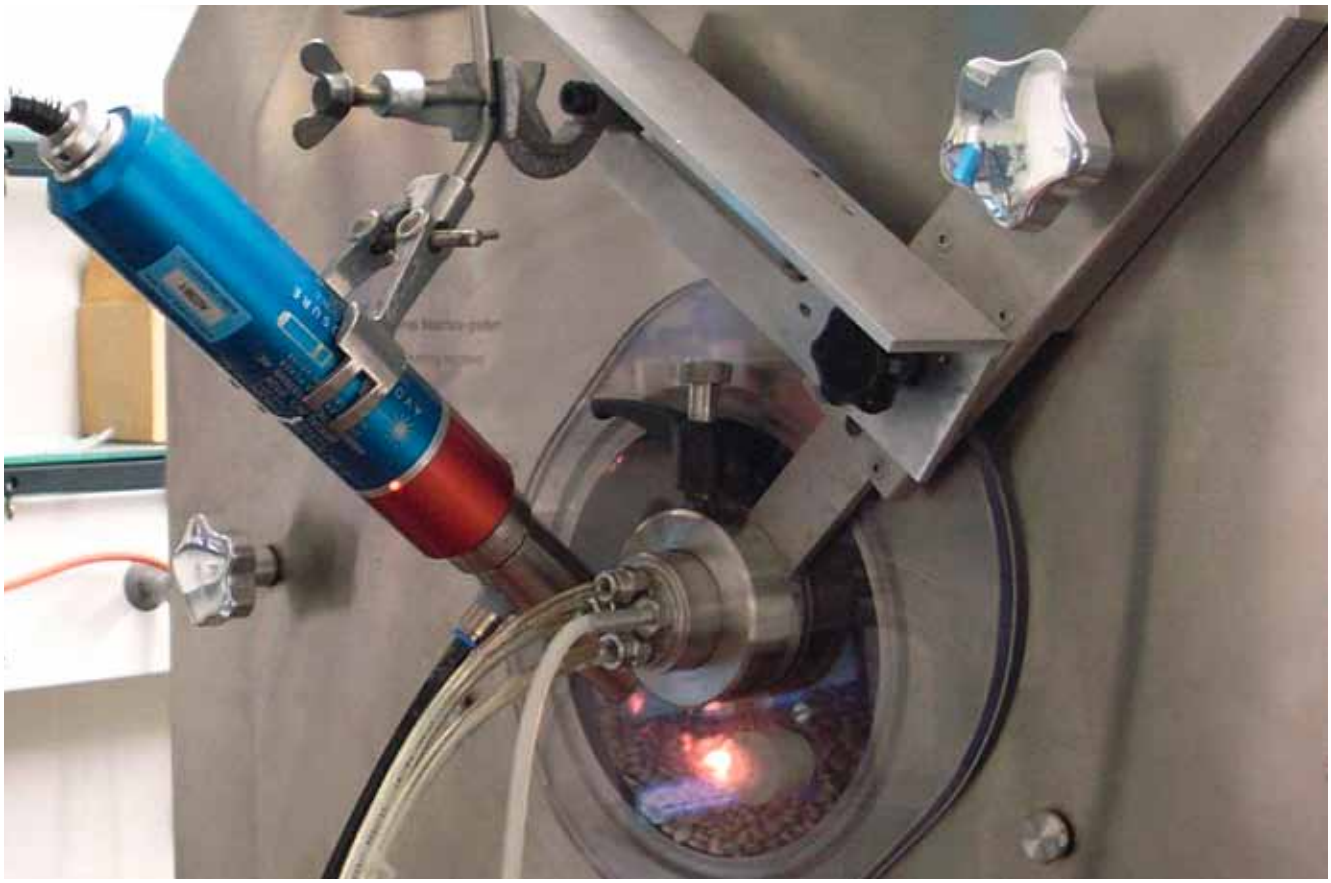


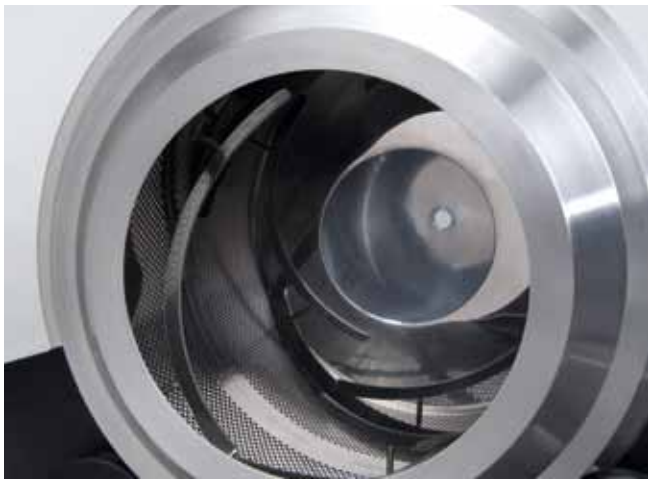
Fig. 1: BFC 5 lab coater with integrated PhAT probe

ied content of diprophylline and correlated linearly with the UV spectroscope values of the same tablets after a model was created. The multivariate regression (PLS, partial least squares) with three major components proved to be a robust method which, in particular, covered the univariate assessment as well. In the sampling range of 0 to 11.2 mg of diprophylline in the coating, the generated PLS model yielded an RMSEC (root mean square error of calibration) value of 0.30 mg of diprophylline and an RMSEP (root mean square error of prediction) value of 0.26 mg.

Inline model

As mentioned above, validation was conducted offline, i.e. a single (coated) tablet at rest was examined by using Raman spectrometry. Inline measurement with a Raman probe integrated into the coater (Fig. 1 and 2) provided a range of variances or problems: during 30 s of measurement, the laser spot of the probe (6 mm Ø) no

Fig. 2: BFC 50 TriPan with integrated PhAT probe



longer falls on a tablet at rest, but rather on a moving tablet bed, i.e. tablets of random orientation or parts of several tablets including the space between them. Depending on the coater drum speed, the tablet bed exhibits different packing densities. The properties of the coating can vary throughout the process. For instance, the refractive index can alter when exposed to different levels of humidity. Even the space between the probe and the tablet bed cannot be maintained exactly during the process thus resulting in changed spectra.

Despite all these influence factors, we managed to describe a coating test in the BFC 5 lab coater by using a generated model (PLS, three major components) [4]. During the process, we also logged inline Raman spectra and correlated them offline with the UV reference data of samples taken at different times (n=6 tablets per sampling time) (Batch A). Another independent batch (Batch B) was coated to test the quality of the generated model. Figure 4 shows the results of both coating tests: diprophylline content predicted by using the model that relied on online Raman data complied well with the actual reference values measured offline. The RMSEP values for Batch A and B was out at 0.26 mg and 0.43 mg of diprophylline respectively. Thus, Raman spectrometry can be employed as a special PAT tool to monitor the coating of tablets in a drum coater.

Scale up

By using the model generated in the BFC 5 lab coater, we monitored the behavior of coating in a BFC 50 TriPan under 30 kg of load distributed between two test batches. The model proved to be applicable to this large coater [5]. In both batches, the amount of applied material complied adequately with the reference values. We obtained an RMSEP value of 0.82 or 0.74 mg of diprophylline respectively. We correctly detected an interruption while coating one of the batches which had no adverse effect on the quality of the model. As the placebo tablets we used were not included in the production batch unlike in the BFC 5 tests, we were able to further improve the model by repeated modelling in the BFC 50 TriPan (as described for the BFC 5). The new model yielded an RMSEP value of 0.55 mg.

Summary

Inline Raman spectrometry can be employed as a special PAT tool to monitor the coating of tablets with substances in a drum coater. A lab-scale model is applicable to the production scale.

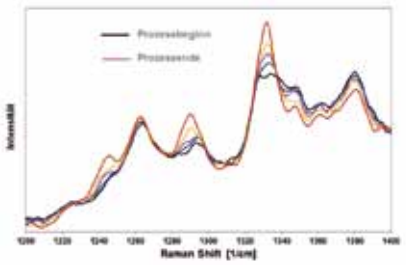


Fig. 3: Raman spectra of tablets during coating

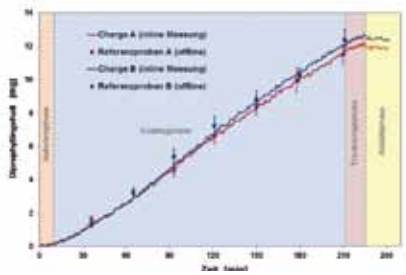


Fig. 4: Diprophylline content determined by Raman measurements during coating; compared with UV reference values (MW±s; n=9)

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