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Real-time assessment of critical quality attributes of a continuous granulation process

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Abstract

There exists the intention to shift pharmaceutical manufacturing of solid dosage forms from traditional batch production towards continuous production. The currently applied conventional quality control systems, based on sampling and time-consuming off-line analyses in analytical laboratories, would annul the advantages of continuous processing. It is clear that real-time quality assessment and control is indispensable for continuous production. This manuscript evaluates strengths and weaknesses of several complementary Process Analytical Technology (PAT) tools implemented in a continuous wet granulation process, which is part of a fully continuous from powder-to-tablet production line. The use of Raman and NIR spectroscopy and a particle size distribution analyzer is evaluated for the real-time monitoring of critical parameters during the continuous wet agglomeration of an anhydrous theophylline – lactose blend. The solid state characteristics and particle size of the granules were analyzed in real-time and the critical process parameters influencing these granule characteristics were identified. The temperature of the granulator barrel, the amount of granulation liquid added and, to a lesser extent, the powder feed rate were the parameters influencing the solid state of the active pharmaceutical ingredient (API). A higher barrel temperature and a higher powder feed rate, resulted in larger granules.

Introduction

Continuous processing is well established in the chemical, cosmetical and food industry, whilst it is still in its infancy in the pharmaceutical industry. Pharmaceutical companies stick to batch processing, because the machinery required for batch processing is already installed in their production plants. A switch to continuous production would require investments in new equipment, training of the employees, new process validation and co-current regulatory documentation. However, batch processing is a very time-consuming and expensive way of production, which can be overcome by continuous production. For example, the development process of solid dosage forms is generally accomplished by the optimization of its production at several batch scales: first, the product is formulated at lab-scale, after which pilot and clinical batches are produced, followed by production scale manufacturing. This up-scaling process is not only costly and time-consuming; it also prolongs the time-to-the-market. Process optimization and validation have to be performed at each batch scale since optimal process and formulation settings at small scale process are generally not transferrable to larger scales [1]. Up-scaling does also involve regulatory issues, because larger batches may require new bioequivalence tests, next to dissolution and stability-tests [2]. Alternatively, continuous production processing allows flexible batch sizes as larger amounts of drug products can be produced by simply running the process longer using the same process equipment. (i.e. “up-scaling in the fourth dimension” [3]). Hence, continuous manufacturing can lead to just-in-time production, where products do not longer have to wait in warehouses. Furthermore, continuous manufacturing lines aim to be fully automated with a minimum of operators, as material transport to the next production step is integrated in the production line. Since pharmaceutical manufacturers are under increasing pressure to reduce expenses and augment efficiency, continuous manufacturing will also have an economical impact.

One of the major reasons for the pharmaceutical industry to be reluctant to move from batch production to continuous production, is the uncertainty of approval by the regulatory bodies.

Indeed, the drug quality and safety have to be assessed and assured at any time. Batch production works with the principle of profound product quality control, by means of sampling and testing after each step in the production process. It is obvious that the current conventional quality control systems of production processes, based on off-line analyses in analytical laboratories, would annul the advantages of continuous processing. Real-time quality evaluation and control, using in-line process analyzers, is crucial for the successful implementation of continuous manufacturing of pharmaceutical products.

Based on the Process Analytical Technology (PAT) -guidance for Industry [4], the Process Validation Guidance for Industry [5] and the ICH guidelines Q8, Q9 and Q10 [6-8], a new approach for pharmaceutical development and production has been proposed. In the PAT-guidance, the FDA encourages the industry to improve pharmaceutical development, manufacturing and quality assurance through innovation in product and process development, process analysis and process control by using the latest scientific advances. The aim is to ensure product quality through the design of effective manufacturing processes, where formulation and process factors and their influence on the end-product are fully understood. This profound understanding and control of manufacturing processes must lead to quality built into the product (Quality by Design). The desire within the pharmaceutical industry to shift towards continuous processing strengthens the need to invest in PAT. The recently introduced Guidance for Process Validation [5] focuses on assuring drug quality by effective process validation. A manufacturing process must be capable of consistently delivering a high quality product. The scientific evidence of that should be based on the collection and evaluation of data, from the process design stage through the commercial production. In the ICH Q8 guideline “Pharmaceutical Development” [6], the principles for building quality into products are stated. Real-time release of pharmaceutical products will be possible if quality of the whole process can be assured by real-time quality control. Q9 “Quality Risk Management” [7] explains the general quality risk assessment and management process and gives examples of possible risk management methods and tools. Naelepää et al. [9] recently showed the application of risk management tools to

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reveal the critical parameters of a coating process. Q10, “Pharmaceutical Quality System” [8], describes a model for an efficient quality management system for the pharmaceutical industry, based on International Standards Organization (ISO) quality concepts. The present study aimed at applying elements of these five guidelines on a continuous pharmaceutical granulation process.

Gamlen and Eardley [10] were the first in 1986 to describe the advantages of continuous processing compared to batch processing. They used a continuous extruder, equipped with two helical mixing blades, for the production of paracetamol extrudates. Lindberg et al. [11] used a twin screw extruder to granulate. Both powder flow rate and liquid flow rate were regularly tested, but not persistently controlled and monitored. The group of H. Leuenberger (University of Basel) developed a semi-continuous agglomeration process, consisting of a high shear granulation mixer and a fluid bed dryer. This system produced mini-batches in a quasi-continuous way [1, 3, 12, 13]. The terminology ‘quasi-continuous manufacturing’ is used here, since the process principle is based on the granulation of small portions of powder in a high shear mixer. After the first portion is granulated, it is discharged to the fluid bed dryer and a second portion is filled into the mixer. This process can hence be considered as a fast succession of mini-batches, but not as a continuous stream of granules.

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As wet granulation is a commonly used unit operation within the pharmaceutical industry to improve compactibility and/or flowability of powder mixtures prior to tabletting, several continuous wet granulation techniques were developed which have been reviewed by Vervaet and Remon [14, 15] Their co-workers [16-19] developed a continuous twin-screw granulator, which is now implemented in the commercially available ConsiGma™-system (GEA Pharma Systems nv., Collette™, Wommelgem, Belgium). Systems producing 25, 50 and 100 kg of granules per hour are commercially available.

This study focused on a high shear twin-screw granulator, being the granulation unit of the ConsiGma™-25 continuous production line. Several equipment, formulation and process factors can

affect the quality of granules manufactured via this technique which will affect further downstream processing, such as the fluid-bed drying and tabletting process step. The continuous granulator parameters were scheduled (Table 1) after Aulton and Banks [20], who listed parameters of a fluid-bed granulation process in three categories: equipment variables, process variables and product variables. Kristensen and Schaefer used the same categories with emphasis on both fluid-bed and high shear mixing-granulation [21].

An evaluation of the equipment, process and formulation parameters having a significant influence upon the critical granule properties is needed in order to find the optimal process conditions. Traditionally, such evaluations are done by trial-and-error, i.e. changing one separate variable at a time (COST-approach). Since this is a time- and product-consuming approach, which does not guarantee finding the optimum conditions [22], the PAT and ICH guidelines recommend the application of organized methods (e.g. design of experiments, DoE) to define the relationship between parameters and quality of the end-product.

A model formulation containing theophylline anhydrate and lactose monohydrate was used to monitor the wet granulation process. Four different polymorphs of theophylline are known: theophylline monohydrate (TH), a metastable form of theophylline and two types of anhydrous forms, one stable at room temperature (TA) and one only occurring at very high temperatures [23]. Pharmaceutical processes can induce (undesired) solid state transformations. Knowledge of the solid state of the API during processing and storage is of the highest importance to assure a safe drug product. Changes in solid state can influence the chemical and physical properties of API's, resulting in different processability (compressibility and powder flow), but also solubility, stability and bioavailability [24]. Norvir, an anti-HIV medicine, was already on the market when in 1998 a polymorphic transformation to a less soluble form of ritonavir was detected [25]. This product had to be reconstituted by the patient, but the dissolution of the capsules failed. Airaksinen et al. [26]

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and Wikström et al. [27] studied the conversion of anhydrous theophylline into theophylline monohydrate using a planetary mixer and a high-shear mixer granulator, respectively.

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The aim of this study was to evaluate which granule properties can be monitored in-line using several PAT-tools (Raman and NIR spectroscopy and a particle size analyzer) during a continuous wet granulation process in the granulation module of the ConsiGma™-25 unit. Furthermore, a DoE was applied to examine the influence of several process and formulation settings upon the granule quality attributes, which were measurable using the implemented PAT tools.

Materials and methods

Materials

Anhydrous theophylline (Fagron Iberica, Barcelona, Spain) (30%, w/w) was granulated with lactose monohydrate 200 M (Caldic Belgium NV, Hemiksem, Belgium). Polyvinylpyrrolidone (Kollidon 30, BASF, Burgbernheim, Germany) was added as binder to the dry powder mixture in a concentration of 2.5% (w/w). Distilled water was used as granulation liquid. Sodiumlaurylsulfate (Fagron, Waregem, Belgium) was added to the granulation liquid (0.5% w/v) to improve the wettability of the dry powder mixture.

Methods

Wet twin-screw granulation

All granules were produced using the ConsiGma™-25 unit (GEA Pharma Systems nv., Collette™, Wommelgem, Belgium) (Figure 1a), which consists of three major parts: a continuous twin screw high shear granulator, a six parallel cell fluid bed dryer and a discharge system. After discharging, a lubricant can be added and blended into the dried granules, after which this mixture can be compressed using an inline tabletting machine.

The continuous granulator unit consists of a barrel with two segments: a feed segment and a work segment, in which the powder is mixed, wetted and granulated. The dosing unit (Figure 1a-(1)) feeds the powder into the granulator (2) in a loss-in-weight-controlled manner. The granulation liquid is fed out of a granulation liquid vessel (3) into two injection nozzles, mounted in the work segment of the granulator, using a loss-in-weight peristaltic pump. The temperature of the work segment can be controlled by a temperature control unit. The wet granules leave the granulator unit through the discharge element of the barrel. The continuously produced wet granules are pneumatically transferred to the six-segmented fluid bed dryer (4). In these segments, the granules are dried by hot air, whose flow and temperature can be controlled. After a set drying time period the granules are subsequently extracted from the drying segment trough a rotational outlet valve. The dry granule output is transferred to a product control hopper (5). Granules are then gravitationally transferred to a mill inlet, which is fed at constant flow by a metering valve. The granules are unloaded gravitationally, after which they can be blended with a lubricant and tabletted.

This study focuses on the continuous twin-screw granulator. The screw configuration was kept constant for all experiments (Figure 1b). The influence of the granulator configuration upon the granule properties will be evaluated in future studies. The screws consisted of a long transport zone and two kneading zones of six kneading elements in an angle of 60°. These two kneading zones were separated from each other by a short transport element, with the same length as a kneading zone. Wet granules were unloaded, from the barrel via another identical short transport element.

Several process parameters can be set for continuous wet granulation (Table 1, 4th column). In this study, bridge breaker speed was held constant at 80%. One of the assets that ConsiGma™ offers is the automatic logging, trending and storage of several process parameters (e.g., temperature granulator barrel, weight powder dosing unit, mass flow granulation liquid etc.).

Twin-screw granulation process monitoring

An in-house made cuvet was placed under the granulator outlet to collect the granules (Figure 2). The cuvet was a box of 10 cm x 10 cm, having a height of 15 cm. One side contained several interfacing places where the NIR diffuse reflectance contact probe could be introduced, while the opposite side of the cuvet contained two interfacing places for the MR Raman probe head. At the inner wall of the cuvet, the Raman probe interfacing holes were covered by quartz-glass, hence allowing non-contact measurements. This measurement setup ensured reproducible probe interfacing and sampling of non-moving granules, hence eliminating variation in the spectra due to variable probe positions. We are currently developing a measurement device for future studies which can be implemented in the transport lines between the different units of the ConsiGma™. This measurement device will allow, similarly as for the cuvet used in this study, static Raman and NIR spectroscopic measurements (as interaction between light and non-moving solids is much more understood) and dynamic Parsum measurements.

Since the equipment produces mainly fines in the start-up phase, the granules produced during the first minute of each granulation experiment were considered as waste and removed. After this first minute, granules were collected in the cuvet for three minutes.

Raman - Spectroscopy

A RamanRxn1 spectrometer (Kaiser Optical Systems, Ann Arbor, Michigan), equipped with an air-cooled CCD detector (back-illuminated deep depletion design) was used. A fiber-optic non-contact probe was placed against the quartz glass at the inner wall of the cuvet in which granules were collected. Spectra were taken via the different interfacing places of the cuvet. The laser wavelength was the 785 nm line from a 785 nm Invictus NIR diode laser. All spectra were recorded with a resolution of 4 cm^{-1} and an exposure time of 30 seconds, using a laser power of 400 mW. Data collection and data transfer were automated using the HoloGRAMS™ data collection software, the

HoloREACT™ reaction analysis and profiling software and the Matlab software (version 7.1, The MathWorks Inc., Natick, Massachusetts).

NIR - Spectroscopy

A Fourier-Transform NIR spectrometer (Thermo Fisher Scientific, Zellik, Belgium, Nicolet Antaris II near-IR analyzer) equipped with an InGaAs detector, a quartz halogen lamp and a fiber optic contact probe was used. Spectra of each granulation experiment were taken, through each of the four interfacing places in the cuvet. The probe was mounted into the cuvet in exactly the same way for every measurement. Hence, measurements could be done in a reproducible way. Each spectrum was collected in the 4500 - 10000 cm^{-1} region with a resolution of 16 cm^{-1} and averaged over 16 scans. Data collection and data transfer were done using Thermo Fisher Scientific's Result Software.

In-line Particle Size Analysis

An In-line Spatial Filter Velocimetry probe (Parsum®, Chemnitz, Germany) was used to continuously monitor the particle size of the granules in-process. The probe consisted of a semiconductor laser diode, which radiated visible light at a wavelength of 670 nm. Furthermore the measurement probe was provided with an integrated air-cleaning system to keep the optical surfaces clean. The applicability and technical details of SFV are extensively described in literature [28]. The probe was placed 10 cm under the granulator outlet and in-line measurements were started after one minute. At the beginning of each granulation experiment one can choose virtual 'sieves', which are the ranges that will be used to calculate the particle size distribution. In this study, the virtual sieves were 150 µm, 250 µm, 500 µm, 710 µm, 1000 µm, 1400 µm, 2000 µm, 3150 µm, 5000 µm and 7500 µm and the particle size distribution was calculated in real-time every five seconds. A shortfall of the Parsum system is that once the particle size distribution ranges are chosen, they cannot be adjusted during the process. This means that prescience on the particle size distribution of the investigated granules is required before starting the SFV measurements. All measurement values were

continuously stored and visualized in real-time by the IPP 70 software. Data analysis was done using the V 1.6 Macro in Excel 2007.

Design of Experiments (DOE)

A 2-level full factorial design was applied to study the influence of four process variables upon both the solid state and particle size (D50) of the wet granules (i.e. 2^4 + 3 = 19 granulations experiments). The screw speed was varied between 600 and 950 rpm. The temperature of the granulator barrel was altered between 25°C and 40°C. The liquid concentration was varied between 8.38% and 9.94% (w/w). The premixed powder was fed in a range from 10 to 25 kg per hour (Table 2). Both the powder feed rate and screw speed determine the barrel filling degree. The center point experiment of the design was repeated three times. All equipment variables (Table 1) were kept constant. The excipients, API and granulation liquid were the same for all experiments. All performed DOE granulation experiments are listed in Table 2.

Data-analysis

The results of the DOE granulation experiments were analyzed using Modde 9.0 (Umetrics, Umeå, Sweden). Simca P+ 12.1 (Umetrics, Umeå, Sweden) was used for principal component analysis (PCA) of the NIR and Raman spectra collected during all granulation experiments. The spectral data were Standard Normal Variation (SNV) corrected for baseline-correction and for neutralizing differences in particle size and packing of the granules before applying PCA.

Results and Discussion

One characteristic of the ConsiGma™-25 is that *all* continuously produced wet granules are transferred to the fluid bed dryer. Granules which are not meeting the predetermined specifications cannot be removed, as is possible for batch production systems. Since batches are inspected after production and off-line tests are performed, bad batches can be rejected and will not be processed

to the next production step. Therefore knowledge and control of the critical characteristics of the granules is important to guarantee appropriate downstream processing.

Particle size

The in-line particle size analyzer (Parsum®, Chemnitz, Germany) gives a very rapid image of the particle size distribution of the continuously produced wet granules. However, during the DoE experiments, sticking of the ***wet*** granules to the probe window (fouling) was observed despite the integrated air-cleaning system. Therefore, only these distributions in which no fouling was seen were extracted from all obtained distributions per DoE experiment (every 5 s during 3 minutes) for further interpretation. For future studies and more detailed wet granule size distribution evaluation, we will first need to examine whether fouling can be avoided by optimizing the probe interfacing and cleaning system. Therefore in this study, only the D50 values from the selected distributions were evaluated to observe some trends how the examined parameters influence the granule size. A representative example of a selected particle size distribution obtained during DoE experiment 4 is shown in Figure 3. The D50 (50 % of the distribution has a particle size smaller than this value) obtained after two minutes of measurements was used as the DOE-response value. Table 2 gives an overview of the D50's after two minutes of production for all DOE-experiments. The influence of the process variables upon the D50 is evaluated in the effect plot, shown in Figure 4. Both the powder feed rate and the temperature of the barrel have a significant and positive influence on the D50. Increasing the powder feed rate and increasing the barrel temperature result in large and oversized granules. Also, a significant interaction between these two factors was found. A higher powder feed rate will result in a higher compaction of the powder in the granulator barrel and thus larger granules. A higher temperature of the granulator barrel will induce a higher solubility of lactose, theophylline and PVP and consequently more bridge formation. Adding more granulation liquid tends to generate larger granules, but only a small range of the amount of added liquid was investigated in this study. Experiments 2, 9 and 19 illustrate these findings, as these three runs

produced very large granules (Table 2). Experiments 1, 4, 6, 12 and 18 produced the smallest granules, as granulation was done using a low powder feed rate (10 kg/hour) and (except for run 18) a cold granulator barrel.

Overall it can be stated that none of the produced wet granules are satisfactory regarding particle size. The produced granules are too large to obtain good tablets after compression, but some remarks should be made. First off all, this is a measurement of wet granules, the particle size of the granules may reduce during drying. Furthermore the ConsiGma™-25 is equipped with a discharging unit, which contains a mill to grind oversized granules. Nevertheless, the aim should be to fully understand, monitor and control the granulation and drying process, so that granules with an ideal particle size distribution are obtained and the mill will be redundant.

Solid State

Raman spectroscopy

Wikström et al. [27] found that Raman spectroscopy is an efficient tool to differentiate theophylline monohydrate from anhydrous theophylline, and that the conversion can be followed in real-time. The spectrum (Figure 5) of TA has two intense peaks at 1664 and 1706 cm^{-1}, whereas TH has a peak at 1686 cm^{-1}, which is due to C=O stretch of the carbonyl-groups. Furthermore during hydrate formation the O==C—N band shifts from 555 cm^{-1} to 572 cm^{-1} [29]. The excipients in the studied formulation have no overlapping Raman signal in these regions.

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Principal component analysis of all spectra collected during the 19 DOE experiments was performed. The spectral regions from 520 cm^{-1} to 600 cm^{-1} and from 1636 cm^{-1} to 1737 cm^{-1} were selected and modeled together, as the solid state information is available in these spectral regions. Three principal components described 99.4% the spectral variation. The first, second and third PC explained 78.62%, 14.37% and 6.41%, respectively. A PC 1 versus PC 2 scores plot was plotted, and

information regarding the solid state can be seen along the PC2-axis. Secondary observation identifiers (i.e., the applied colors in the scores plots) were assigned to each individual spectrum (score) in order to classify them after used screw speed, barrel temperature, liquid concentration and powder feed rate. When classifying spectra according to the amount of added granulation liquid (Figure 6a; the red triangles correspond to the spectra collected from the DOE experiments where 8.38% (w/v) granulation liquid was used, the green crosses to 9.16% (w/v) and the blue squares to 9.94 % (w/v)), clustering can be noticed in the scores plot. Granules, which were produced with a low concentration of granulation liquid, are mainly situated in the positive part of the PC2, whilst those granulated with a high amount of liquid are situated in the negative part. Classification according to the applied barrel temperature (Figure 6b) shows, that granules produced in a barrel heated to 40°C result in spectra mainly clustered in the positive half of the PC 2. Granules produced using a cold barrel (25°C) can be found in the negative part of PC 2. Concerning the powder feed rate, the positive part of the PC2 contains most of the runs, where a powder feed rate of 25 kg/hour was used (Figure 6c). When data were classified after screw-speed, no clustering could be seen in the scores plot.

To find an explanation for these clusterings, one should take a look at the loadings plots. No solid-state clustering can be seen along the PC1-axis from the scores plots, but only along the PC2-axis. This indicates that the variation in solid state is expressed by PC 2. The loadings plot of the first principal component shows basically the joint spectra of theophylline monohydrate and anhydrous theophylline. The variation captured by PC 1 is most probable due to altering measurement conditions between the different analyzed samples (e.g., differences in probe to sample distances, differences in physical properties and granule sizes of the different samples etc.). More interesting is the loadings plot of the second principal component (Figure 7). Maxima are found at 555 cm^{-1}, 1665.6 cm^{-1} and 1707.6 cm^{-1}, whereas minima are found at 574.2 cm^{-1} and 1687.5 cm^{-1}. Both minima can be attributed to theophylline monohydrate, while the three maxima can be assigned to anhydrous theophylline. Hence, experiments where the spectra are clustered in the positive part of

the PC2-axis contain a quantity of remaining anhydrous theophylline. These experiments are listed in Table 3.

It is clear that water, and a certain water activity is needed for the conversion of anhydrous theophylline to theophylline monohydrate. Hence, the presence of remaining anhydrous theophylline can be explained for the runs with lower liquid concentration. Adding less water, which results in a lower water activity, leads to a lower conversion rate of anhydrous theophylline to theophylline monohydrate [30, 31].

Ticehurst et al. [30] stated that at higher temperature an increased water activity is required to transform anhydrous theophylline to theophylline monohydrate. This can explain why runs with a higher barrel temperature result in these small remaining amounts of anhydrous theophylline in the granules. Furthermore hydration is an exothermic process, which means adding energy by means of heat will shift the reaction towards the anhydrate form [32].

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With a high barrel filling the granulation liquid will have more difficulties to spread well through the powder bed, this can be an explanation of remaining anhydrate when granulating at 25 kg/h. Furthermore a high barrel filling will result in larger granules (as stated earlier), which makes it harder for the granulation liquid to penetrate in the granules.

Raman spectroscopy together with Design of Experiments showed to be valuable tools to investigate and understand solid state transformations in wet granules. Even small amounts of a non-expected polymorph can be detected.

NIR spectroscopy

To investigate if the same conclusions can be made when analyzing the granules with NIR spectroscopy, runs 6 till 19 were taken into account (runs 1 till 5 were not taken into account, since inadequate NIR spectra were obtained due to sampling problems). PCA was performed on the complete spectral range (10000 to 4500 cm^{-1}) resulting in three principal components. These

explained 97.1 % of the variation. PC 1 explained 69.11 % of the spectral variation, PC 2 18.82% and PC 3 9.13 %. In order to make a distinct classification possible, secondary observation identifiers (i.e., assignment of colors, which are corresponding to certain process settings, to the scores) were added to all spectra.

The first principal component differentiates the granulation experiments after water content (Figure 8a). Granules produced with a high liquid amount are spread along the positive part of the PC 1-axis, while those produced with a low liquid amount can be found in the negative part of PC 1. This is confirmed by the loadings of this first principal component, which clearly shows two water bands (Figure 8b). The spectral band at 5222 cm^{-1} corresponds to the OH-stretching and bending vibrations of water molecules, while the 7035 cm^{-1} band can be attributed to first overtone OH-stretching vibrations. Two more vibration are contributing to these peaks, resulting in two shoulders at 6880 cm^{-1} and 5168 cm^{-1}. These two bands are caused by lactose monohydrate [33].

In Figure 9a, the PC 2 versus PC 3 scores plot was plotted and data were labeled and examined after secondary observation identifiers. Most spectra of the granules produced with a low concentration of granulation liquid can be found in the positive part of the PC 3-axis. The same trend can be seen for granules produced in a warm granulation barrel (Figure 9b). Classifying data after powder feed rate or screw speed did not result in any clear clustering.

The loadings plot of PC 3 (Figure 9c) shows an absorption band of OH vibrations at 7035 cm^{-1}. This water-bond is oppositely directed, compared to the bands at 5947 cm^{-1} and 6009 cm^{-1}, which are specific peaks for anhydrous theophylline. Furthermore, a remarkable peak at 5168 cm^{-1} can be attributed to lactose monohydrate, which has the same concentration in all granules [33]. NIR confirms hence the Raman analysis findings. The granulation experiments corresponding to the scores in the positive part of the PC3-axis most likely contain remaining anhydrous theophylline. NIR only shows the variation in solid state, when different barrel temperatures or liquid concentrations are applied.

An overview of the runs containing an amount of anhydrous theophylline is given in Table 3. Runs (6-19) which were thought to contain anhydrous theophylline when investigated with Raman are all confirmed by NIR.

Conclusions

This study gave an insight in the possibilities of implementing PAT-tools in a continuous twin-screw granulation process. Both Raman and NIR showed to be appropriate tools for understanding the solid state behavior of theophylline during wet granulation. Peak differentiation and polymorph differentiation was more definite in Raman spectra than in NIR spectra.

The In-Line Particle Probe showed to be a promising tool for the in-line measurement of particle size distribution. More investigation on the measurement technique will be necessary to obtain adequate measurements of wet granules. The main challenge is to avoid fouling of the optical surfaces.

Performing a DOE, allowed to reveal the most influencing granulation parameters upon granule size and the solid state of the API. The temperature of the barrel and the added amount of granulation liquid, and to a lesser extent the powder feed rate showed to have an effect upon the solid state of the wet granules. The powder feed rate and the barrel temperature had significant effects upon the granule size.

This paper proves that at-line measurements of both solid state and particle size during a continuous twin-screw granulation process are feasible. Given these promising results of the presented tools, the next step will be the design of a new process analyzer interfacing device. This device should permit integration of PAT-tools in the ConsiGma™-25, allowing them to provide real-time information. Future studies will focus on the use of the in-line measured critical process and product information to steer the next process steps (e.g., feed forward adjustment of process settings of further process steps).

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Declaration of interest

The authors report no declarations of interest.

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Gewijzigde veldcode

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Tables

Equipment Variables	**Product Variables**		**Process Variables**
	Starting Powder Properties	**Liquid Characteristics**	
Screw configuration	Particle size distribution	Viscosity	Powder feed rate
Screw length	Homogeneity of raw material powders	Surface tension	Bridge breaker speed
Length- to-diameter ratio of the screws	Presence of agglomerates in premix	Solid-liquid tension	Filling degree of barrel
Diameter of the granulation liquid inlet nozzels	Segregation during feeding		Screw speed
	Powder density		Barrel temperature
Powder feeding method	Cohesion	*Binder type*	Liquid feed rate
Place of liquid addition into barrel	Particle shape	*Binder concentration*	
	Surface roughness	*Binder addition method (wet/dry)*	Powder feed rate
	Surface area		
	Solubility in granulation liquid		
	Hygroscopicity		
	Wettability		
	API/excipient quantitative ratio		
	Concentration		

Table 1: Equipment, Product and Process Variables influencing the characteristics of a continuous twin-screw granulation process.

Run Order	Screw Speed (rpm)	Powder Feed Rate (kg/h)	Water Content (%)	Barrel T (°C)	D50 (µm)
1	950	10	8,38	25	2397
2	600	25	9,94	40	5793
3	950	10	9,94	40	3299
4	950	10	9,94	25	2521
5	950	10	8,38	40	3650
6	600	10	9,94	25	2843
7	775	17,5	9,16	32,5	3787
8	950	25	8,38	40	3966
9	950	25	9,94	40	6153
10	600	25	8,38	25	2463
11	950	25	9,94	25	3188
12	600	10	8,38	25	2051
13	600	25	9,94	25	3053
14	600	10	9,94	40	2437
15	775	17,5	9,16	32,5	3124
16	950	25	8,38	25	3227
17	775	17,5	9,16	32,5	3097
18	600	10	8,38	40	2383
19	600	25	8,38	40	4137

Table 2. Overview of the design experiments – Calculated D50 values obtained after two process minutes.

Run	Water Content Dry - (8,38%)	Barrel T Hot - (40 °C)	Powder Feed Rate Full - (25kg/h)	Raman	NIR
1	X				
2		X	X	+++	
3		X		+++	
4					
5	X	X		+++	
6					
7					
8	X	X	X	+++	+++
9		X	X	+++	+++
10	X		X		
11			X		
12	X				
13			X		
14		X			
15					
16	X		X	+++	+++
17					
18	X	X		+++	+++
19	X	X	X	+++	+++

Table 3. Overview of all DOE granulation experiments. Both significant parameters and spectroscopic responses are listed. Runs in which Raman and/or NIR-spectroscopy show the presence of anhydrous theophylline are indicated with +++.

Figure 1a

Figure 1b

Figure 2

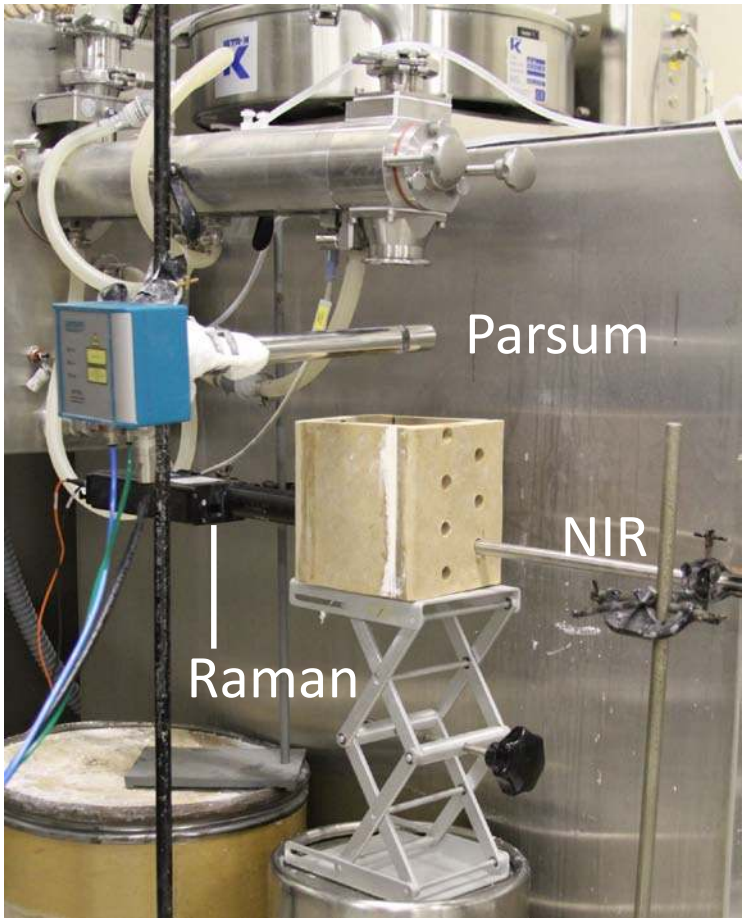

Figure 3

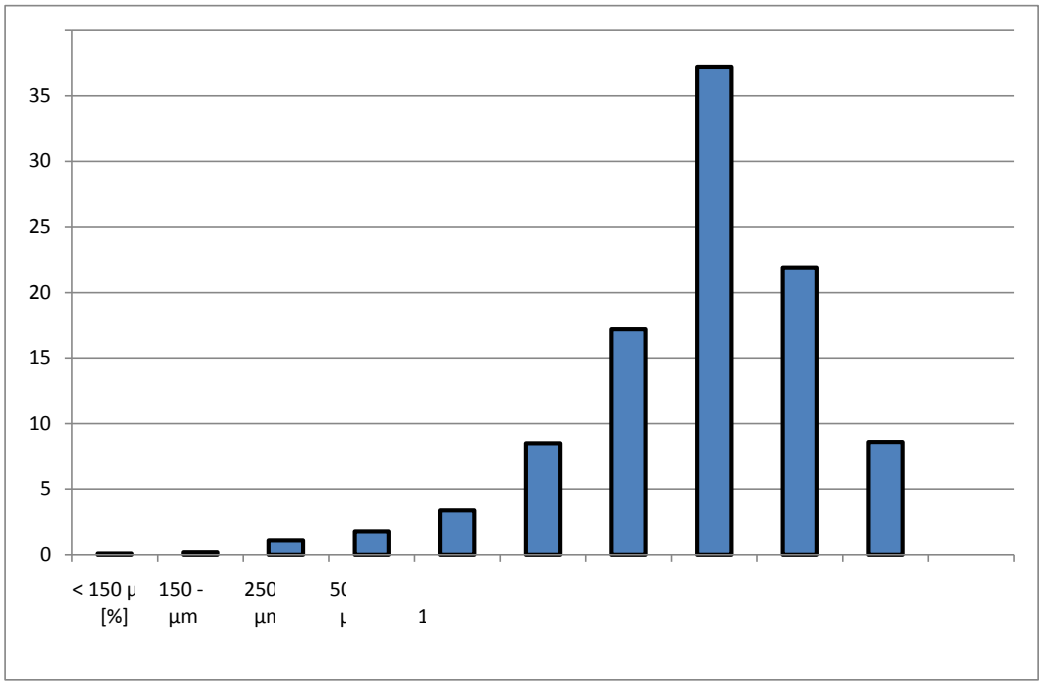

Figure 4

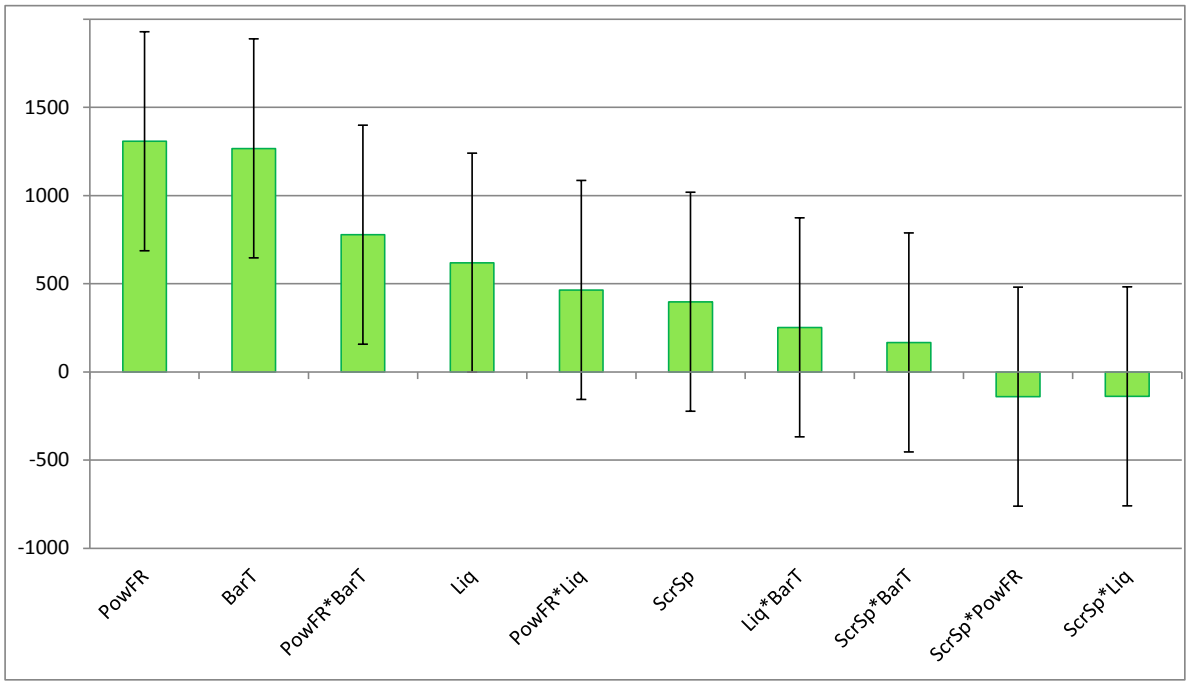
1500
1000
500
0
-500
-1000
PowFR
BarT
PowFR*BarT
Liq
PowFR*Liq
ScrSp
Liq*BarT
ScrSp*BarT
ScrSp*PowFR
ScrSp*Liq

Figure 5

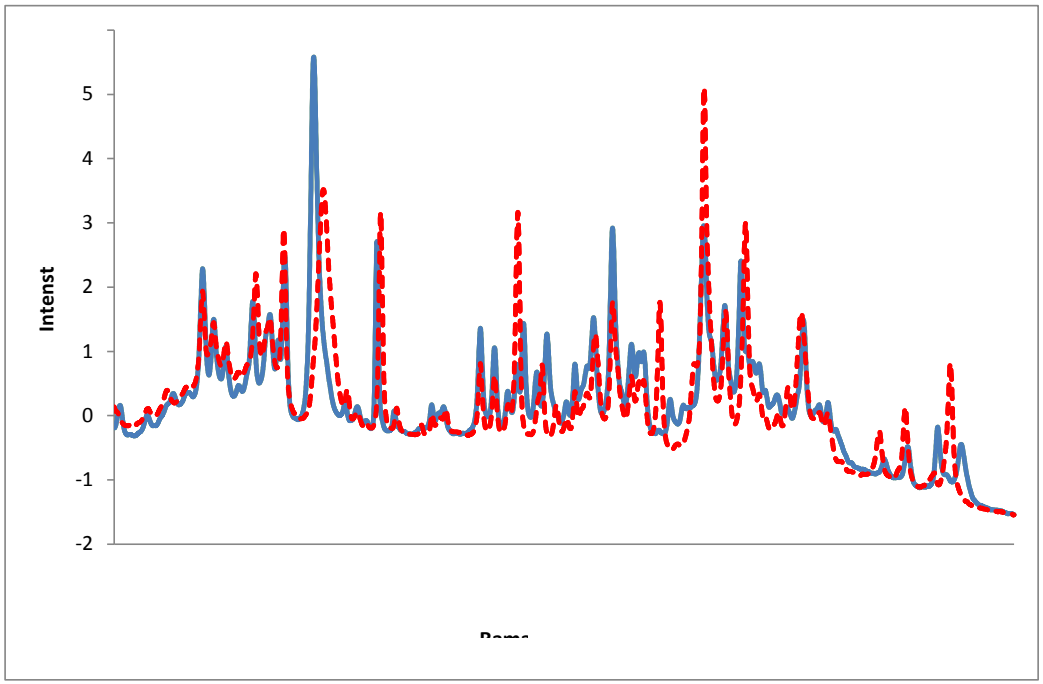

Figure 6a

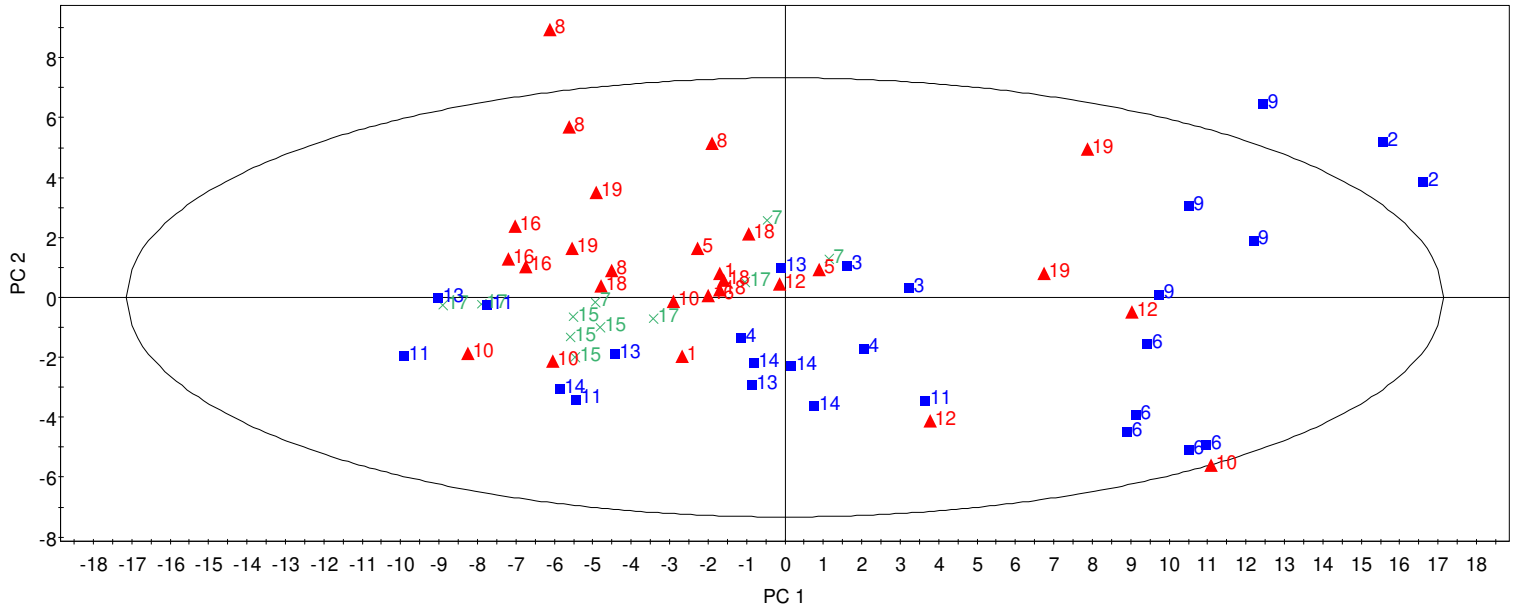
PC 2
PC 1
8
6
4
2
0
-2
-4
-6
-8
-18 -17 -16 -15 -14 -13 -12 -11 -10 -9 -8 -7 -6 -5 -4 -3 -2 -1 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18

Figure 6b

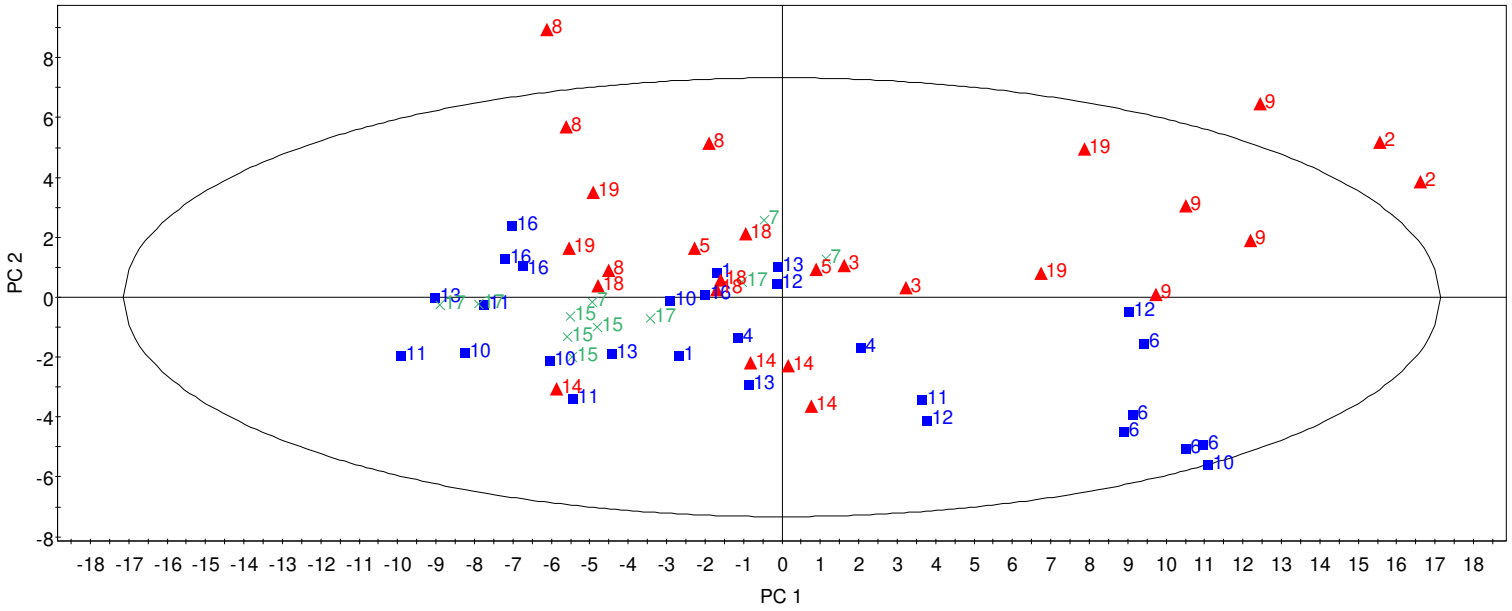
PC 2
PC 1
8 6 4 2 0 -2 -4 -6 -8
-18 -17 -16 -15 -14 -13 -12 -11 -10 -9 -8 -7 -6 -5 -4 -3 -2 -1 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18

Figure 6c

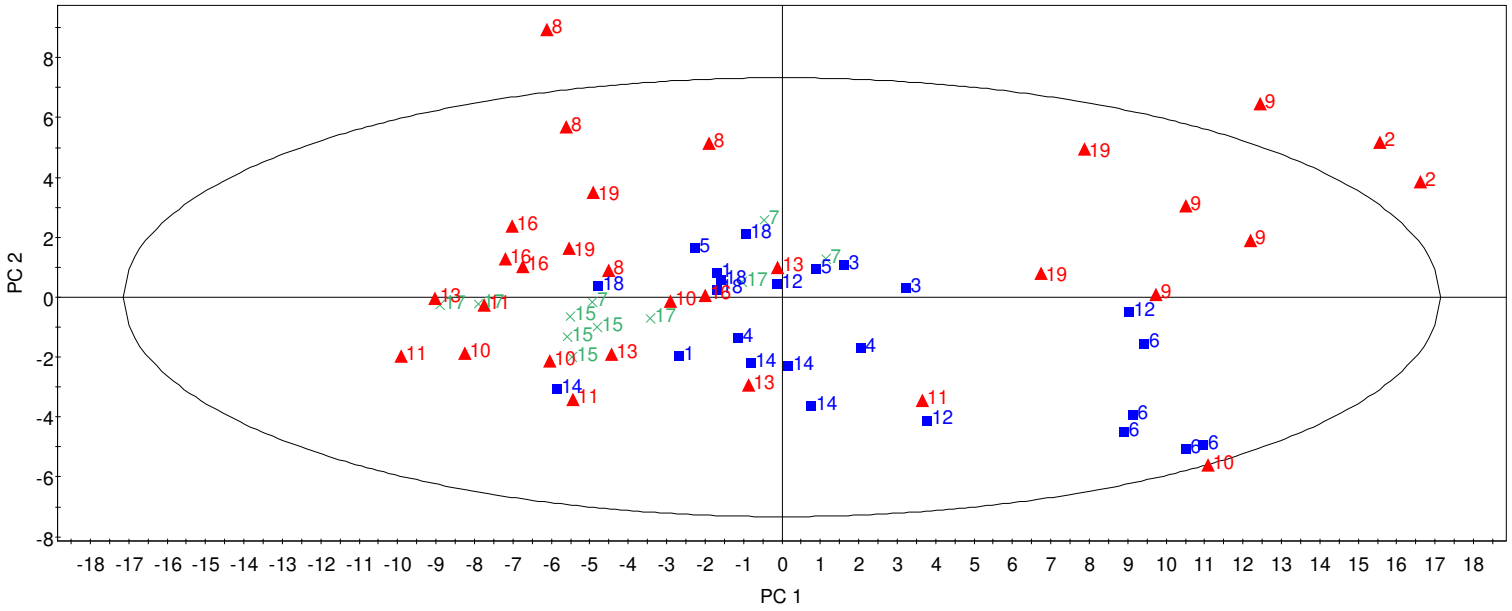
PC 2
PC 1
8 6 4 2 0 -2 -4 -6 -8
-18 -17 -16 -15 -14 -13 -12 -11 -10 -9 -8 -7 -6 -5 -4 -3 -2 -1 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18

Figure 7

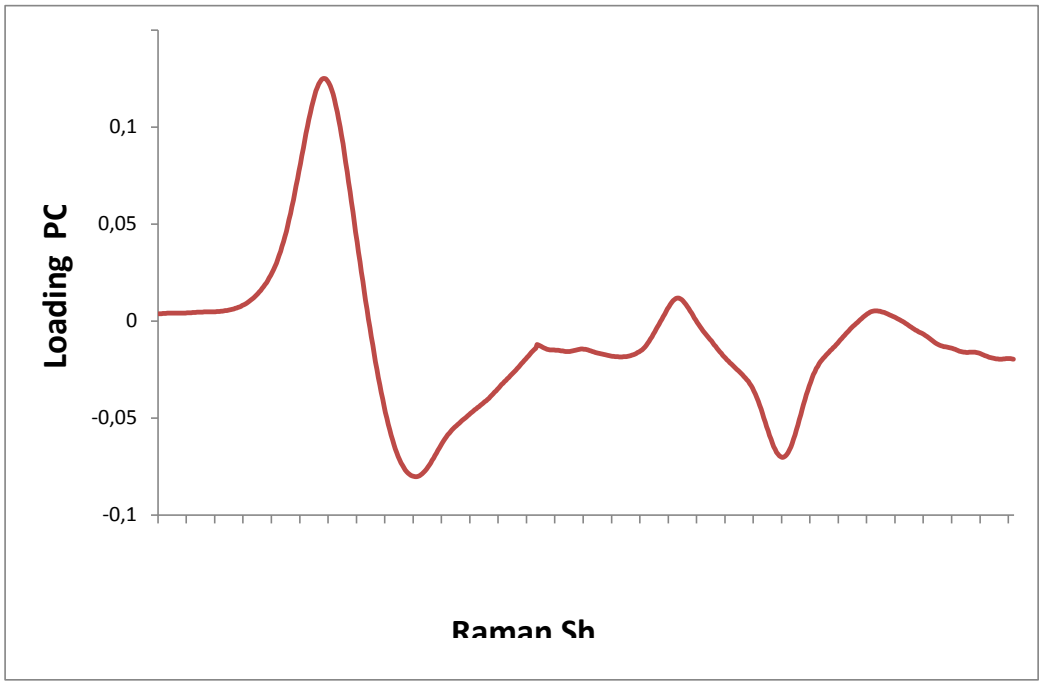

Figure 8a

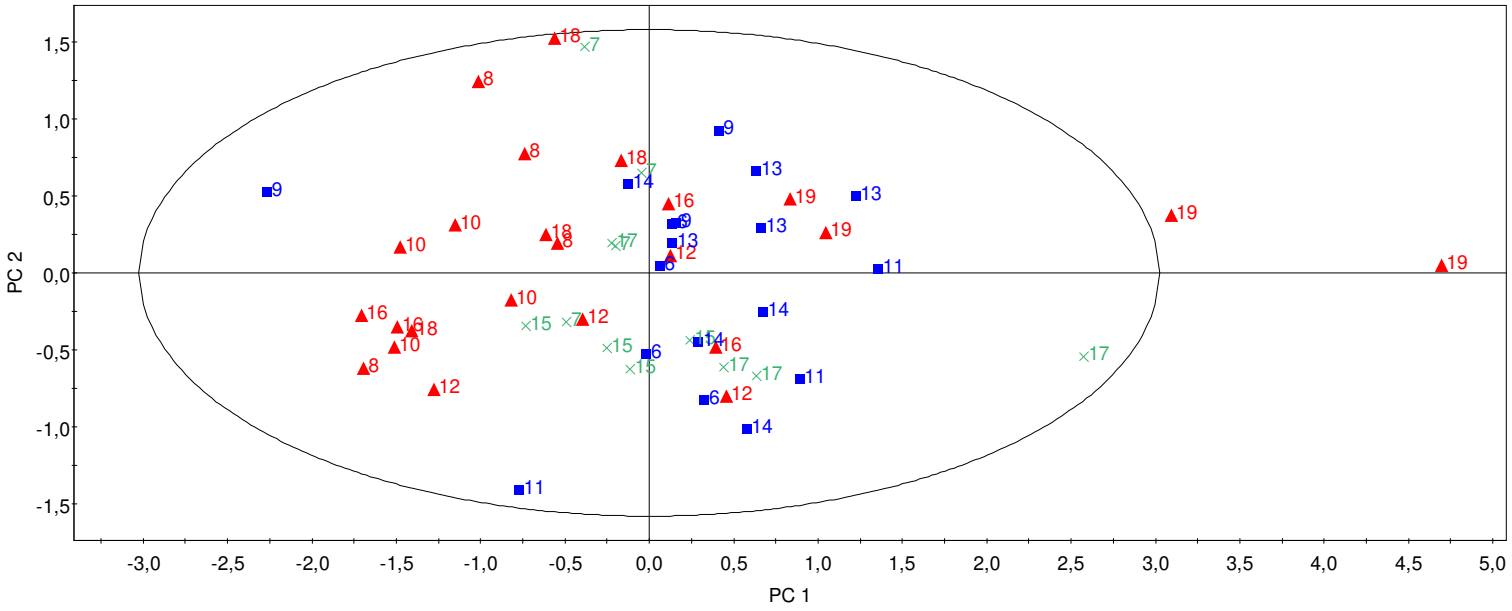
PC 2
PC 1
1,5
1,0
0,5
0,0
-0,5
-1,0
-1,5
-3,0
-2,5
-2,0
-1,5
-1,0
-0,5
0,0
0,5
1,0
1,5
2,0
2,5
3,0
3,5
4,0
4,5
5,0

Figure 8b

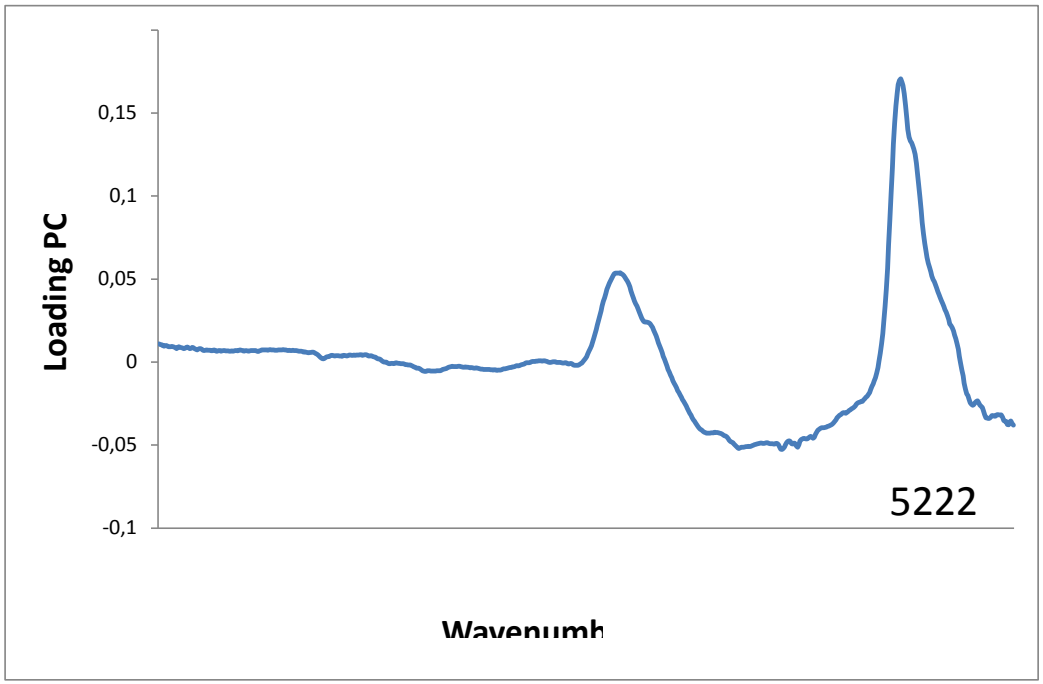

Figure 9a

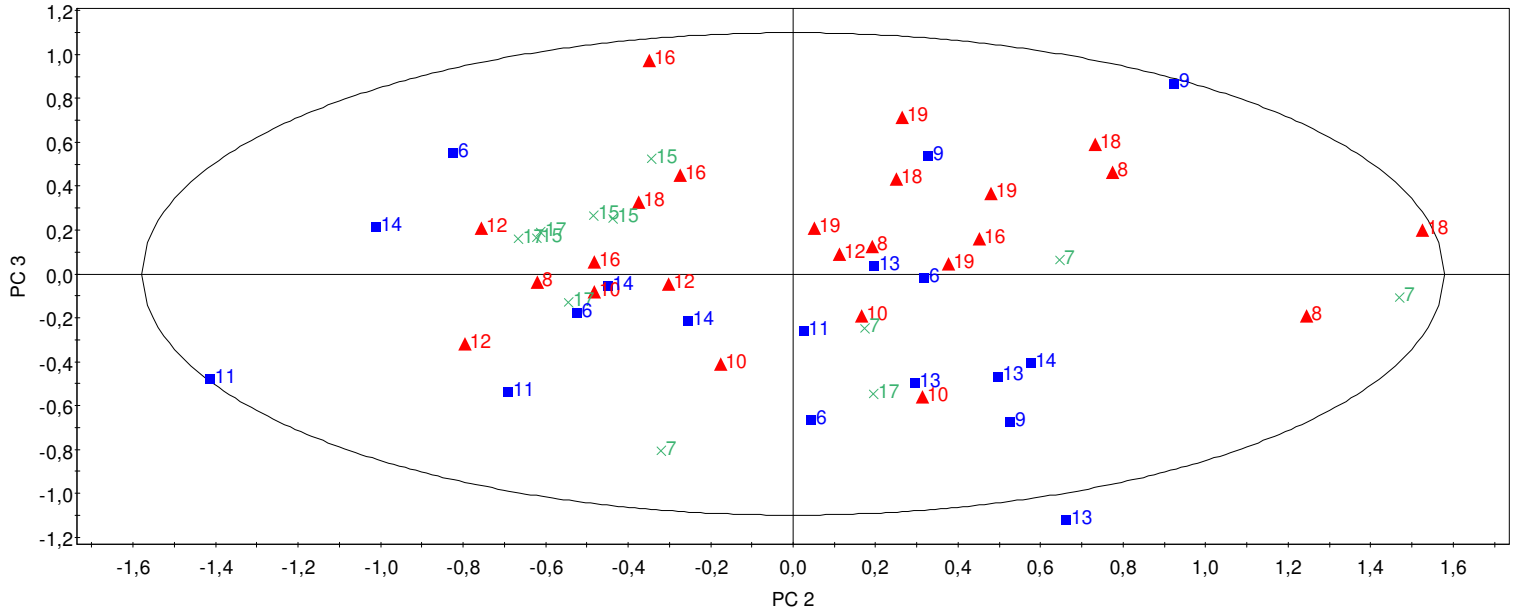
PC 3
PC 2
1,2
1,0
0,8
0,6
0,4
0,2
0,0
-0,2
-0,4
-0,6
-0,8
-1,0
-1,2
-1,6
-1,4
-1,2
-1,0
-0,8
-0,6
-0,4
-0,2
0,0
0,2
0,4
0,6
0,8
1,0
1,2
1,4
1,6

Figure 9b

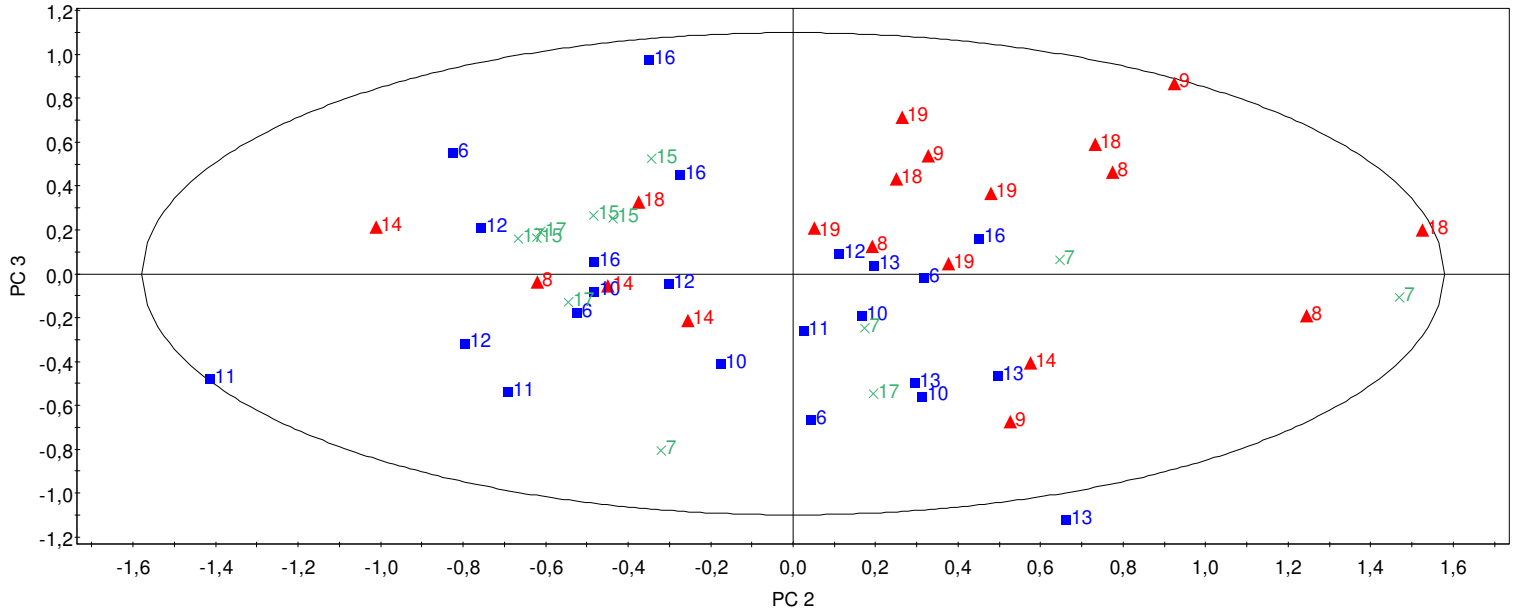
PC 3
PC 2
1,2
1,0
0,8
0,6
0,4
0,2
0,0
-0,2
-0,4
-0,6
-0,8
-1,0
-1,2
-1,6
-1,4
-1,2
-1,0
-0,8
-0,6
-0,4
-0,2
0,0
0,2
0,4
0,6
0,8
1,0
1,2
1,4
1,6

Figure 9c

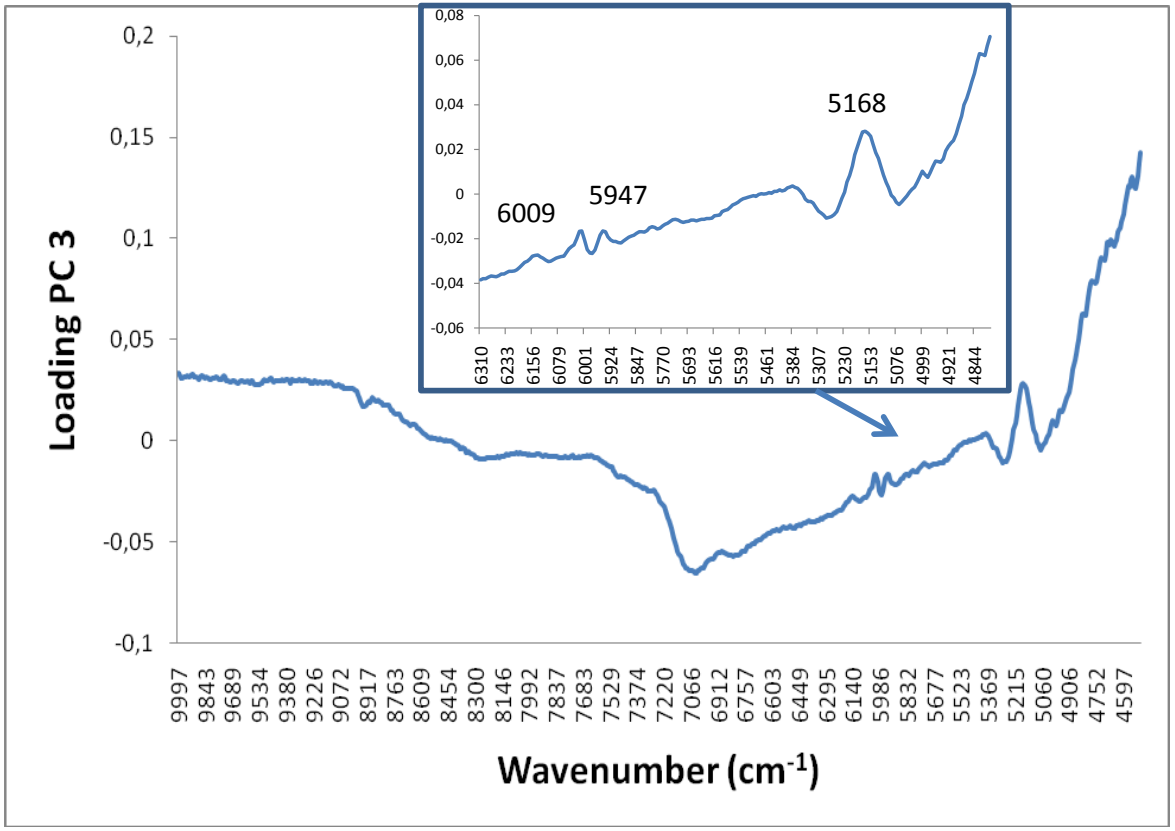
Loading PC 3
0,2
0,15
0,1
0,05
0
-0,05
-0,1
9997
9843
9689
9534
9380
9226
9072
8917
8763
8609
8454
8300
8146
7992
7837
7683
7529
7374
7220
7066
6912
6757
6603
6449
6295
6140
5986
5832
5677
5523
5369
5215
5060
4906
4752
4597
Wavenumber (cm-1)
0,08
0,06
0,04
0,02
0
-0,02
-0,04
-0,06
6310
6233
6156
6079
6001
5924
5847
5770
5693
5616
5539
5461
5384
5307
5230
5153
5076
4999
4921
4844
6009
5947
5168

Figure captions

Figure 1a. ConsiGma™-25

(1) Continuous feeder - (2) Continuous twin screw high shear granulator – (3) Granulation Liquid Vessel - (4) Six parallel cell fluid bed dryer – (5) Product control hopper with integrated mill

Figure 1b. Screw configuration of the twin screws.

Figure 2. In-line twin-screw granulation monitoring. An in-line Spatial Filter Velocity probe (Parsum®) was placed under the outlet of the granulator and above the cuvet, allowing the dynamic measurement of particle size distribution from the produced granules. A Raman probe and an NIR-probe were implemented at several locations in the cuvet allowing static measurements of the granules.

Figure 3. Particle size distribution observed during DOE experiment 4.

Figure 4. Effect plot of the response variable D50.
PowFR: Powder feed rate; BarT: Temperature of the granulator barrel; Liq: Granulation liquid concentration; ScrSp: Screwspeed

Figure 5 : SNV-corrected Raman spectra of anhydrous theophylline (full line) and theophylline monohydrate granules (dashed line) in lactose

Figure 6a. Raman spectra: PC 1 (78.62 %) versus PC 2 (14.37 %) scores plot (a) colored according to concentration of added granulation liquid. Red triangles – 8.38 %; blue squares – 9.94 %; green crosses centerpoints – 9.16%.

Figure 6b. Raman spectra: PC 1 (78.62 %) versus PC 2 (14.37 %) scores plot (b) colored according to the applied temperature of the barrel. Red triangles – 40°C; blue squares – 25°C; green crosses centerpoints – 32.5 °C.

Figure 6c. Raman spectra: PC 1 (78.62 %) versus PC 2 (14.37 %) scores plot (c) colored according to powder feed rate. Red triangles – 25 kg/h; blue squares – 10 kg/h; green crosses centerpoints – 17.5 kg/h.

Figure 7. Raman spectra: Loadings plot of the second principal component (14.34 %)

Figure 8a. NIR spectra: PC 1 (69.11 %) versus PC 2 (18.82 %) scores plot: (a) colored according to added granulation liquid amount. Red triangles – 8.38 %; blue squares – 9.94 %; green crosses centerpoints – 9.16%.

Figure 8b. NIR spectra: Loadings plot of the first principal component (69.11 %).

Figure 9a. NIR spectra: PC 2 (18.82 %) versus PC 3 (9.13 %) scores plot (a) colored according to concentration of added granulation liquid. Red triangles – 8.38 %; blue squares – 9.94 %; green crosses centerpoints – 9.16%.

Figure 9b. NIR spectra: PC 2 (18.82 %) versus PC 3 (9.13 %) scores plot (b) coloured according to the applied temperature of the barrel. Red triangles – 40°C; blue squares – 25°C; green crosses centerpoints – 32.5 °C.

Figure 9c. NIR spectra: Loadings plot of the third principal component (9.13 %) with a zoom on the 6310 cm^{-1}-4800 cm^{-1} region.