Heinrich Heine
Universität
Düsseldorf

From process understanding and monitoring to advanced process control: application to pharmaceutical continuous manufacturing

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Morgane Jelsch
from Mulhouse, France

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from the institute for Pharmaceutical Technology and Biopharmacy
at the Heinrich Heine University Düsseldorf

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Supervisor: Prof. Dr. Dr. h.c. Peter Kleinebudde
Co-supervisor: Prof. Dr. Jörg Breitkreutz

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The best view comes after the hardest climb.

Unknown author

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Frequently used abbreviations

API: active pharmaceutical ingredient

BU: blend uniformity

CM: continuous manufacturing

CPP: critical process parameter

CQA: critical quality attribute

CU: content uniformity

CV: controlled variable

DAF: drying airflow

DAT: drying air temperature

DRS: drying rotation speed

DV: disturbance variable

EPT: event propagation time

FBD: fluidized bed dryer

FBRM: focused beam reflectance measurement

FDA: Food and Drug Administration

FOTC: first order time constant

HPLC: high-performance liquid chromatography

LOD: loss on drying

LC: label claim

LS ratio: liquid to solid ratio

MRT: mean residence time

MPC: model predictive control

MV: manipulated variable

NIRS: near infrared spectroscopy

OOS: out of specification

PAT: process analytical technology

pCPP: potential critical process parameter

PI: proportional integral

PID: proportional integral derivative

PSD: particle size distribution

QbC: Quality-by-Control

QbD: Quality-by-Design

QbT: Quality-by-Testing

RTRT: real-time release testing

RTD: residence time distribution

TSG: twin-screw granulator

PLS: partial least square

PoE: penalty on error

PoM: penalty on move

WG: wet granulator

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1 Introduction

1.1 Continuous manufacturing

1.1.1 Current state

Continuous Manufacturing (CM) is an innovative approach for pharmaceutical manufacturing where material is simultaneously charged and discharged from the process [1]. In fact, input raw materials or mixtures are continuously fed into a process train while the processed output materials are continuously removed [2]. The continuous process allows to work with small equipment and the batch size is then proportional to the process run time. In an end-to-end continuous pharmaceutical manufacturing process, different process steps are sequenced together to form a continuous production line where product removal can occur at the same rate as the input of raw materials [2]. A pharmaceutical manufacturing process consisting of a combination of batch and continuous process steps is also considered as continuous manufacturing [2].

An increasingly number of recent publications from pharmaceutical science is focused on continuous manufacturing for drug product manufacturing and several pharmaceutical companies have invested for dedicated continuous manufacturing facilities [3]: Novartis [4, 5], Pfizer [6] and Eli Lilly [7]. Moreover, collaborations between industry and academy have been developed around the continuous manufacturing topic: for example, the Novartis/MIT partnership resulted in the production of Aliskiren in an end-to-end process which included continuous solid oral dose formulation [8].

The regulatory administrations such as the FDA have been encouraging and supportive for the development and use of such a technology, with guidance and guidelines for industry [9].

1.1.2 Regulatory perspectives

The regulatory agencies such as the Food and Drug Administration (FDA) or the European Medicines Agency (EMA) regulate pharmaceutical drug products to ensure a continuous supply of high-quality drugs over the world. They currently encourage a change in manufacturing practices in favor of *cleaner, more flexible, and more efficient* manufacturing of drug products, as supported by ICH Q8 (R2), Q9, Q10, and Q11 and the introduction of QbD concepts as well as science- and risk-based approaches to assure product quality [2, 10-18].

The starting point for discussions about continuous manufacturing versus batch manufacturing was the definition of a lot and of a batch [1]. According to the Code of Federal Regulations, 21 CFR 210, a batch is defined by a specific quantity of a drug or other material that is intended to have uniform character and quality, within specified limits, and is produced according to a single manufacturing order during the same cycle of manufacture. Also, a lot is defined as a batch, or a specific identified portion of a batch, having uniform character and quality within specified limits. Thus, the definitions of batch and lot are applicable to both batch manufacturing and continuous manufacturing as they refer to the quantity of material intended to have uniform character & quality [1, 2, 16].

Continuous manufacturing is consistent with Quality by Design (QbD) efforts of FDA and ICH [15, 10] and has the potential to improve the assurance of quality but also agility, flexibility, cost and robustness in the development of pharmaceutical manufacturing processes [17]. Over the past decade, there have been significant advancements in science and engineering to support the implementation of continuous pharmaceutical manufacturing. Continuous manufacturing enable quality to be directly built into process design [1, 17]. In parallel, the progress in process analytical technology (PAT) for designing, analyzing, and controlling manufacturing led to scientific and regulatory readiness for continuous manufacturing [17, 18].

The FDA and ICH guidelines [11-14, 18] collectively reinforce the adoption of a more systematic and integrated framework in order to reach an increased level of process understanding and product knowledge. Process understanding, control strategies, plus on-line, in-line, or at-line measurement of critical quality attributes (CQA) can support control strategies that include real time quality evaluation, which would be equivalent to, or better than, laboratory-based testing on collected samples [18].

Both pharmaceutical industry and regulatory agencies gain more experience with continuous manufacturing over time, leading to new regulatory aspects to explore and also to early and frequent communication between both parties [2].

The current regulatory documents suggest the following considerations for CM: FDA Guidance on Process Validation [19] encourages the use of quality risk management, and quality systems at all stages of the manufacturing process lifecycle linking product and process development; while the ICH Guidelines introduce the concept of continuous process verification thanks to PAT tools for process monitoring and/or control. Most recently, FDA Guidance on CM quality considerations [9] has been focusing on the CM process dynamics and control strategy.

In its draft guidance from 2019 [9], the FDA defines the two key concepts for CM processes: the definition of batches and the understanding of the process dynamics in order to apply a control strategy. This control strategy should be based on the following:

- Input materials control, in order to characterize the flow behavior and the residence time distribution (RTD),
- Process monitoring, in order to gather accurate real-time information,
- Material diversion, in order to waste of out-of-specification (OOS) material depending on process dynamics.

With a great amount of generated data that should be evaluated in real time to make process decisions, CM processes imply the introduction of automated systems. According to the FDA [9], the design and validation of these automated systems will be particularly critical.

Concerning process development, there is no particular pre-defined manufacturing strategy but some considerations should be included for regulatory submission: flow rate of material through the process, total process operation time, critical process parameters and their ranges, IPC points and also specific information about development and modeling of the continuous process where a robust control strategy is crucial for a consistent quality of product over time (e.g. residence time

distributions, system dynamics, disturbance propagation, information on model set up, maintenance, and model improvement) [2, 9].

Moreover, CM control strategy also includes several aspects [1, 2, 9, 13, 18, 19]:

- State of control: to ensure the consistency of the final drug product quality and of the process performance over the production time through appropriate process attributes or ranges for monitoring or a multivariate process control approach. The detection of process disturbances and introduction of corrective actions to bring the process back into conformance could help to maintain the final drug product quality. Sudden or uncontrolled changes in a process variable should be considered as well as start-up, shutdown and transient phases. Process disturbances may occur during development on a reproducible operation for a certain period of time and criteria should be developed to define the state of control.
- Raw materials and intermediates: to follow the quality attributes of raw materials and intermediates linked to the product CQAs along the process through deep product and process understanding with the use of PAT tools (e.g. in-line, at-line, or on-line). The determination of the characteristics of an intermediate product may be more difficult in a continuous process due to the limited sampling ports and high sampling frequencies.
- Equipment: to ensure their performance with special maintenance, calibration and periodic review as equipment may need to run for long periods of time.
- Process monitoring and sampling: to manage planned changes and respond to unplanned disturbances. Sampling strategy should be addressed: appropriate sampling frequency (i.e. appropriate to the dynamic response time of the parameter or attribute), sample acquisition time, flow rate, residence time distributions, “blind” times (e.g. refill of the hoppers), number of probes and their distribution have impact on the design of the test for quality along the process.
- Traceability: materials flow along the line should be understood, documented and supported by data on system dynamics such as residence time distributions at relevant flow rates and operating conditions. If OOS material is produced, the tracking of material flow in the system is crucial for further process decisions that may end in material diversion.
- Product collection or rejection: pre-defined criteria and procedures of collection of rejection should be established. In situations where the state of control is lost from process disturbances, a portion of the batch (or in worst case, the whole batch) may be rejected from the line.
- Risk assessment and specifications: to ensure the product formed is of uniform quality and character. The understanding of the risks of the process helps to setup a risk mitigation strategy for a process robustness.

The key in continuous manufacturing is to have clearly defined criteria, which describe state of control operation, and to understand the process dynamics for different aspects: sampling strategy, traceability of the materials, process monitoring with possible material diversion, etc.

1.1.3 Benefits

Continuous manufacturing offers several advantages and opportunities for pharmaceutical manufacturing improvements [1-3, 16]. From an operator's perspective, the first thing to notice is the significantly reduced size of the process operation units. In fact, the whole concept of continuous manufacturing lies in production over time. Batches and lots are defined by total production time. This way, CM allows to work with smaller equipment and facilities leading to a smaller ecological footprint, more flexibility, lower costs and more environmental friendly pharmaceutical production. It also leads to a safer and more efficient process: reduced manual handling with fewer processing steps and shorter turnover time leads to reduced risk of human error and reduced occurrence of deviations [16]. In fact, smaller size for reactors (e.g. extruders) allows to drastically change the surface-to-volume ratio in favor of increased heat removal capabilities leading to more control over the process and it limits the amount of material in the process line, which is safer with dangerous or toxic reagents [20, 21].

Continuous manufacturing allows enhanced development approach with quality-by-design (QbD) and process analytical technology (PAT) for on-line monitoring and control for increased product quality assurance in real-time. With the concept of residence time distribution, CM also facilitates real-time release testing (RTRT) and innovative manufacturing aspects such as risk-based control strategy that enables quality to be directly built into process design [22].

From an economical perspective, the use of continuous manufacturing can result in yield improvements, especially where synthetic routes are not possible in batch mode [3]. CM processes can be more efficient in energy savings and reduced solvent consumption, which lead both to more economical and more ecological processes.

1.1.4 Challenges

Continuous manufacturing is a new approach in the pharmaceutical industry. Many advantages have been presented in the upper section but it comes also with new challenges such as the development of more accurate and more appropriate process monitoring.

The integrated process line requires to better understand the interactions between unit operations, to ensure stable operation and to understand the impacts of residence time distributions and of the propagation of changes and disturbances through system. It is also necessary to implement an integrated data acquisition system with analytical tools to the control system in order to support implementation of feed-back or feed-forward control with advanced data management tools [1]. It then raises the question of sampling. For satisfactory process monitoring, the operators need to "see" what is performed during the process, thus representative sampling procedures need to be considered in order to describe the process and to consistently assure product quality over time, with the definition of sample size, sampling frequency and location of sampling probes [1, 9].

FDA supports the implementation of continuous manufacturing using a science and risk-based approach [9]. Enhanced process understanding is needed for further continuous manufacturing development. Mechanistic models for all processing steps could be very useful but are not systematically available yet and multivariate analysis for determination of drug product quality

should be implemented in the future. This is why, control strategy implementation should be highly supported with for example, appropriate in-process controls (IPC), real time release testing (RTRT) and/or automated systems for process monitoring and control. PAT should demonstrate the ability to detect and manage process disturbances.

The beauty of continuous manufacturing implementation lies in the cross-sectional study and efforts across engineering, advanced analytical chemistry, process automation and process modeling technical functions [3]. In fact, process automation and control systems together with online PAT are required to check the state of control of some process parameters such as mass flow rates. Non-destructive on-line PAT tools can give feedback on process parameters in real-time [3].

1.2 Process units[1]

The presented work in this thesis takes over some open questions left from the previous PhD student Victoria Pauli from the University of Düsseldorf in collaboration with the Continuous Manufacturing group at Novartis Pharma AG, Switzerland. The experimental part has been performed on the same process equipment thus parts of this section have been previously published in Victoria Pauli's thesis [23] and papers [44, 46].

1.2.1 Connected process line

Figure 1 shows a flow-chart of a typical fully connected wet granulation continuous manufacturing process line [1, 16, 23, 24]. The process units from dosing to drying will be further developed in the following sections.

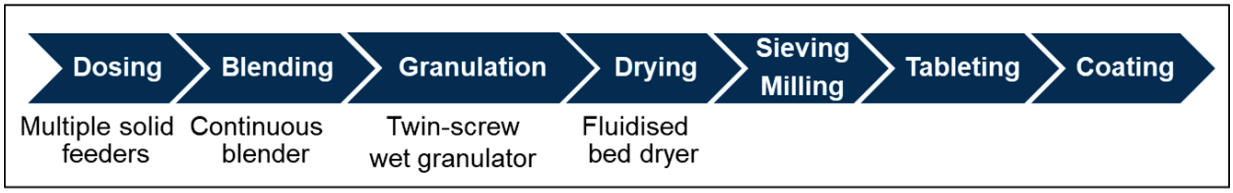

Figure 1: Flow-chart of a classic continuous wet granulation process line for film coated tablets and examples of equipment units.

1.2.2 Feeding

Multiple solid feeders can deliver to the next operation unit either individual formulation components or pre-mix of a part of the final formulation, both at a defined mass flow rate. Accurate and steady dosing is essential for the quality and robustness of final drug product.

Typical powder feeders can either operate in gravimetric mode by loss-in-weight control or in volumetric mode by fixing the screw speed; nevertheless, this last option is not the preferred one as the flow properties of bulk powders can lead to wrong powder distribution, hence wrong solid

[1] Parts of this section have been previously published in former PhD student Victoria Pauli's thesis "Development and Implementation of a Redundant Process Control Strategy in Pharmaceutical Continuous Manufacturing"

ratio. The usual gravimetric feeding works with rotating screws dispensing powder from a hopper into the next unit operation with a defined ratio and a defined throughput from few grams to dozen of kilograms per hour (see section 1.3.1, page 20 for details concerning formulation). The actual feed rate is monitored by a weighing cell, associated with a control unit adjusting the screw speed according to the readings and the set points. [25-27].

1.2.3 Blending

When multiple solid feeders are setup in the line, a continuous blending unit is needed to ensure a proper content uniformity, bulk powder sizes, stickiness, moisture or any other physical or chemical property that needs to be homogenized in the final blend. Blend uniformity can be monitored by process control systems using PAT (see section 1.4.1, page 23 for further details).

One of the typical blender designs is the convective continuous blender: fixed impellers on a rotating shaft induce the particle movement through a horizontal cylinder. Different types of impeller and cylinder are available depending on the process uses [28, 29]. Continuous mixers compared to batch blenders are superior in their ability to homogenize segregating mixtures [30]. In case of complex formulations, batch blending could be done in a large enough container by weighing all ingredients and blending by mechanical agitation over a suitable period of time. This is sometimes the preferred option as it would be too difficult to feed separately each ingredient in the continuous blender, as the process line growth is limited by room space.

1.2.4 Granulation

Depending on the product, the granulation step can either be wet or dry, respectively with or without a liquid in the process. Several techniques exist; for wet granulation: continuous twin-screw wet granulation, spray drying or fluidised bed granulation, and for continuous dry granulation: twin-screw melt granulation or roller compaction to name a few [31-35]. All available methods for continuous wet granulation shared that after being delivered by powder feeders and/or continuous blender, the powders have to be wetted and agglomerated successively or simultaneously and that the resulting wet granules have to be dried. The most important and most frequently used granulation processes were relying on fluidized-bed or twin-screw granulation techniques [34, 36]. Fluidized-bed granulation offers agglomeration and drying in a single machine with the inconvenience of long process time for the agglomeration step [37]. Wet granulation can be done via twin-screw granulators but an additional drying step is required.

Granulation is a major step of the process as it fixes a lot of parameters by agglomerating particles into granules; for example, the API content (*i.e.* the ratio between API and excipients) or the granules characteristics (*e.g.* bulk density, hardness, moisture, compressibility, etc), which can highly impact the final drug product quality attributes. It helps to increase homogeneity by reducing risk for segregation. Granulation improves the overall processability and flowability by enlarging the particles through the following agglomeration process: wetting, nucleation, coalescence, consolidation and attrition. Also, the resulting granules are free of dust: the amount of fine particles has been drastically reduced by agglomeration [38-41].

The used continuous wet granulation technique in this presented thesis is continuous twin-screw wet granulation (TSG), which consists in a horizontal barrel containing co-rotating screws and being continuously fed by the previous mentioned powder blend and by the granulation liquid. The design of the co-rotating screws is of high importance as it defines the shear forces applied to the materials while it travels through the barrel.

The screw configuration together with the formulation are determinant to define the granules characteristics (*e.g.* porosity). The screw configuration can be adapted depending on the process needs by assembling different screw elements on a shaft. Other process parameters are involved in the granulation process like the total solid flow rate, the rotation speed of the co-rotating screws and the liquid-to-solid ratio (L/S). The total solid flow rate and the rotation speed have an impact on the material residence time and on the TSG fill-level, thus on the applied shear forces: granule size distribution can be impacted. L/S ratio has an impact on the agglomeration process: depending on the water amount, granules aspect can cover the range from powder to paste [42, 43].

These process parameters are dependent on the investigated formulation (materials and proportions) and they are engaged in the granules critical quality attributes (*e.g.* bulk/tapped density, particle size distribution) [43, 44]. This leads to a careful formulation and process development, evaluating each critical process parameter (CPP) for each CQA in order to draw process interactions and potential process models for advanced process control.

Continuous wet granulation using twin-screw granulator at high temperature helped with a poorly compactible drug, with minimum amounts of excipients used, to enhance tabletability [45].

1.2.5 Drying

Once the wet granules have been created via TSG, they leave the barrel to the drying phase. Fluidized-bed dryers are largely used for continuous drying in pharmaceutical industries. Some studies investigated moisture content prediction [46-48] with good correlation between the observed and expected thermal energy loss via applied mass-energy balance principle or other mathematical models.

Continuous fluidized bed drying consist in a vertical drying system supplied by air of pre-defined temperature and flow rate [47, 49]. Recently, two drying systems have been marketed: GEA ConsiGma™ or Glatt GPCG 2 CM fluidized-bed dryer. The first one consists in a segmented fluidized-bed dryer containing six separated, identical, static drying chambers operated in a semi-batch mode where wet granules are filled into the chambers by a rotating inlet valve [50]. The second one provides a fluidized-bed dryer with ten rotating chambers where wet granules are subsequently but continuously filled and are fluidized; eight chambers are simultaneously used for granules drying and the two remaining chambers are used either to discharge granules once drying is done or to wait for next granules to come from the extruder. In this case, the drying time of the material inside the fluidizing chamber is defined by the rotation speed of the dryer [44, 51].

After drying, granules can be processed further by sieving, milling or mixing with additional components before being compressed to produce tablets. Tablets can be coated. Those process operation steps are not described in this thesis as they are out of scope.

1.2.6 Powder transfer system

Powder transfer systems (PTS) are necessary to ensure the continuous flow of wet or dry material across the process operation units. For short distances (e.g. between TSG and dryer), it might be sufficient to transfer wet granules by blowing pressurized air. For longer transfer distances or in case of upward transfer (e.g. from powder containers to dosing units when hoppers need to be refilled), vacuum PTS can be required.

1.3 Pharmaceutical development

1.3.1 Formulation

The solid oral dosage forms like tablets are usually made up of two parts: the Active Pharmaceutical Ingredient (API) and a mix of excipients. The excipients have the function to guarantee the dosage, to support or enhance the stability of the drug product and the bioavailability of the API [52, 53]. In other words, defining the formulation of a drug product is equivalent to shape its behavior. Excipients recommendations for batch manufacturing are applicable to continuous manufacturing.

Over the past decades, more attention was paid to the innocuity of the processed excipients mix as it should not interfere with the body and create adverse effects. Moreover, pharmaceutical industries seek for no interactions between excipients or with the API because it could potentially change the effectiveness of the medicine and even increase toxicity. With the large number of substances on the market and the diversity of their sources and process functions, the toxicity assessment of the excipients has been broadening [53-55]. The simpler the better, it has been suggested to simplify the formulations as much as possible by reducing the number of excipients to strictly meet the required functions [55].

The excipients can be classified based on their functions in dosage form. For solid dosage forms, there are various functions like binders, diluents, lubricants, disintegrating agent's, plasticizers, etc. Some excipients like starch play different roles depending on the amount in the formulation [53].

The choice of the excipients mix in the formulation could be in agreement with the concept of QbD. The selected excipients should ideally be chemically stable, non-reactive (both to human body, to other excipients and to API), non-toxic, with low sensitivity to process or equipment and preferably economical [53].

1.3.2 Critical Quality Attributes of solid oral dosage forms

ICH Q8 guideline defined the critical quality attributes (CQA) as "a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality" [11]. The identification of CQAs should be done through risk assessment [12], based on the experience gained in the laboratory phase for example, and it would result in a list of CQAs ranked in order of importance. Then, the product design and

design space can be defined. Thus, it is possible to carefully design the product formulation and process to meet the product attributes: critical material attributes (CMA) and critical process parameters (CPP) have a great impact on the CQAs and they contribute to identify and control the different sources of variability in CQAs [56].

By evaluating each CPP for each CQA with the use of PAT tools, process interactions and potential process models can be drawn for advanced process control. Quality control strategy for continuous manufacturing should be based on the real-time assessment of the intermediates and final product CQA [43].

1.3.3 Quality-by-Design

In traditional batch mode, the quality is generally tested at the end of a process step, usually when product is discharged from the process unit, which leads to Quality-by-Testing (QbT). Pharmaceutical continuous manufacturing with the use of PAT tools is suitable for an enhanced development of Quality by Design (QbD): a comprehensive QbD approach allows for continuous improvement through product and process understanding to ensure better product quality [17, 56-60].

QbD is described by FDA guidance as "building in quality into the final product by understanding and controlling formulation and manufacturing variables: testing is used to confirm the quality of the product" [9]. ICH Q8 guideline supports the idea of defining QbD as a systematic approach and introduces the concept of design space [11]. In fact, QbD becomes more flexible with multidimensional combination and interaction of input variables (e.g. material attributes) and wider range of material attributes and process parameters. Thus the identification of the CQAs with their associated CMAs and CPPs is crucial for QbD implementation.

Both regulatory perspectives align on the importance of QbD being tackled through deep process understanding (e.g. relationships between CPP and CQA). Several aspects need to be taken into account for a proper QbD: the identification of target product profile, the determination of product critical quality attributes with links to raw material attributes and to process parameters, risk assessment, design space, design and implementation of a control strategy and the product lifecycle management and continuous improvement [61, 62].

The control strategy should be based on CMAs and CPPs states, which should be observed and monitored via the appropriate PAT tools, in order to compensate their variability.

1.3.4 Quality-by-Control

One step forward is the Quality-by- control (QbC) concept, which is an important extension and complementary approach of QbD, where quality is built into the process via deep process knowledge and process modelling. This ultimate control strategy aims for an efficient and active control of the CPPs to achieve targeted CQAs, for more robustness of the process and less product quality variability. The active control advocated by QbC would be based on enhanced product and process knowledge as well as advanced model-based techniques including data reconciliation, model predictive control (MPC) and risk analysis [63].

Continuous manufacturing offers the appropriate framework to develop QbC concept with regard to the design of continuous manufacturing, the amount of generated data in real-time and the possibility to build and control quality while drug product is being processed. Moreover, QbC aims for real-time automatic and optimal control of CQAs thanks to the identification of dynamic relationships between CQAs and CMAs or CPPs. It aims for real time release and minimized production of OOS products.

The benefits would be significant with automatized process decisions and quality assurance [41]. It would also lead to more sustainable, more agile and adaptable processes in the pharmaceutical industry [42].

1.3.5 Industry 4.0

Quality-by-Control can open the door to the next-generation smart manufacturing or Industry 4.0, which is based on digitalization and automation to improve manufacturing processes by evaluating real-time data. The concept of Industry 4.0 is driven by technological advancements, supports sustainable value creation and leads to more agile, smart and personalized pharma industry. It is thought to overcome the challenge of the increased amount of data collected in the pharmaceutical industry for data integrity, in particular with the introduction of artificial intelligence (AI) and cloud-computing [64].

With the increased amount of data available, and the need to evaluate those data in real-time for continuous manufacturing, it is necessary to develop new ways as digitalization to collect, sort out, classify and treat data: “transforming current pharmaceutical manufacturing to Pharma 4.0 (i.e. Industry 4.0) requires a new approach to manufacturing and process data capture” [65]. These massive amounts of data produced in real-time could be used for different manufacturing objectives: for example, to increase process understanding, to improve process control strategies or to optimize production plan [66].

Applying Industry 4.0 as a new concept for sustainable and agile processes can improve the effectiveness of coordination and communication across different entities within the process line, mitigate waste and pollution at different stages and enable a more autonomous decision-making process [64].

Continuous manufacturing combines the concept of continuous process improvement as defined in ICH Q10 and Q12 guidelines with the digitalization opportunities provided by Industry 4.0. Industry 4.0 aims to upgrade the entire operation system to become smarter, more flexible and sustainable processes; this is in agreement with the values promoted by continuous manufacturing. Moreover, one of the keys to Industry 4.0 application is the integration of PAT tools [18] for continuous improvement through process knowledge obtained from generated data. This would lead to advanced process control strategies via process monitoring, process modelling and process control in order to predict and anticipate failures such as OOS products.

1.4 Process control strategies

1.4.1 Process analytical technology

Continuous manufacturing is a highly innovative technology, capable of developing cutting edge process control strategies for pharmaceutical industry [9]. Several techniques have been developed in order to understand, monitor and control the process. Continuous manufacturing is designed to use an integrated systems approach for the control of pharmaceutical product quality in real-time. According to the FDA [67], quality of pharmaceutical drug products should be by design or should be built-in through a comprehensive understanding of the process. The tools proposed for process understanding are based on multivariate data analysis, real-time process analyzers, process control and continuous improvement systems towards Industry 4.0 [64].

The risk-based regulatory approaches recognize the level of scientific understanding of how formulation and manufacturing process factors affect product quality and performance as well as the capability of process control strategies to prevent or mitigate the risk of producing a poor quality product. Indeed, product quality and performance are ensured through the design of effective and efficient manufacturing processes; moreover, product and process specifications are based on a mechanistic understanding of how formulation and process factors affect product performance for continuous real time quality assurance.

The process analytical technologies (PAT) are aiming to develop and implement effective and efficient innovative approaches in pharmaceutical development, manufacturing and quality assurance. The final product quality can be ensured by means of PAT tools measuring critical quality attributes of raw and in-process materials [67]. FDA guidance gives the regulatory framework for PAT-tools. Figure 2 gives a schematic representation of the possible measurements methods with examples [68-70]:

- in-line: measurement where the sample is not removed from the process stream and can be invasive or noninvasive, typical method: near-infrared spectroscopy (NIRS);
- on-line: measurement where the sample is diverted from the manufacturing process, and may be returned to the process stream, investigated method: high-performance liquid chromatography (HPLC) [71] or focused beam reflectance measurement (FBRM) imaging (crystal size, shape) [72];
- at-line: measurement where the sample is removed, isolated from, and analyzed in close proximity to the process stream, typical methods: in-process control (IPC) for tablets such weight, thickness, and crushing force tests.

Fast and non-destructive methods are preferred (e.g. in-line or on-line measurement techniques) but regular sampling of small amounts for potentially destructive at-line method can be considered as a reasonable PAT implementation. Pharmaceutical industry is using PAT tools to understand, monitor and/or control e.g. the API content, the LOD and the PSD as CQA of the intermediates and final drug products.

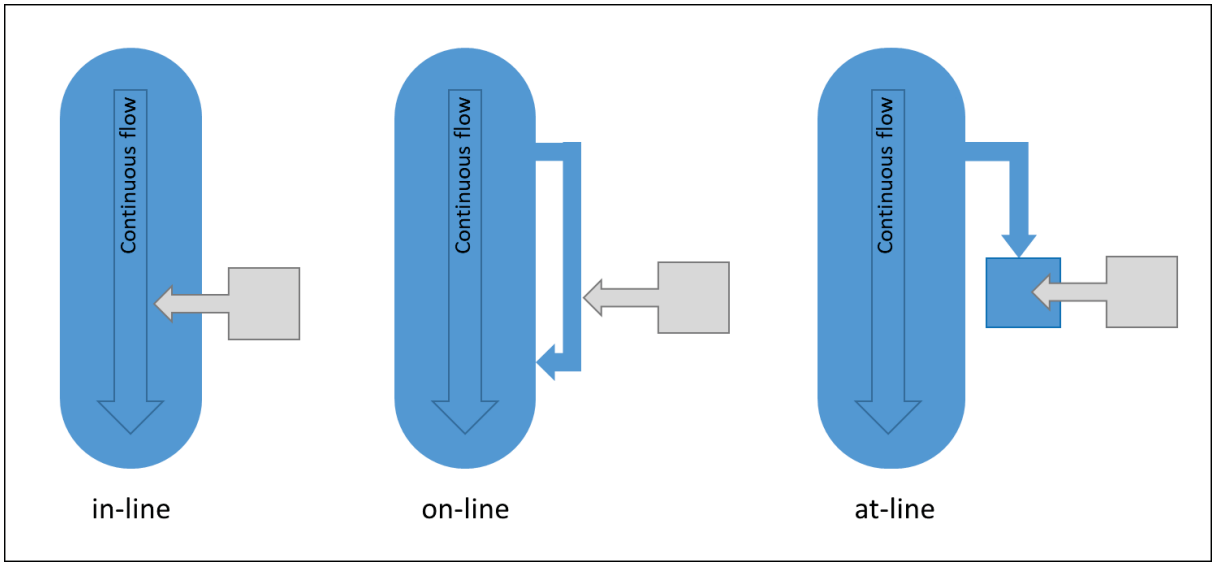

Figure 2: Schematic representation of the different PAT strategies with in-line, on-line and at-line measurements; adapted from [73].

1.4.2 Near-Infrared Spectroscopy

Near-infrared spectroscopy (NIRS) is a molecular vibrational spectroscopic technique studying vibrational transitions in molecules [74]. It is a fast and non-destructive method that can be implemented in continuous manufacturing as in-line method in order to follow the different critical process and product attributes in real-time. It measures the vibrational properties of a given sample and absorption intensities are compared between sample and its reference, for example:

- the comparison with API reference is calibrated to the sample API concentration, after the method being calibrated via HPLC as reference analytics;
- the comparison with spectral water bands is calibrated to the sample moisture content after the method being calibrated via LOD measurements as reference analytics.

In addition, this method does not require any sample preparation, which makes it easier to implement in a continuous process line [75].

Concerning particle size distribution (PSD), several techniques have been investigated in different studies for at-line, on-line and in-line measurements:

- focused beam reflectance measurements (FBRM) as at-line method where a focused laser beam scans across particles [36, 76],
- laser diffraction (LD) where a dispersed sample passes through a laser beam and its reliable use is limited to opaque particles larger than 50 µm [77],
- NIRS as in-line method where molecular vibrational transitions are measured and are calibrated to the PSD via Dynamic Image Analysis [78, 79],
- Parsum probe as in-line method, based on the principle of spatial filter velocimetry, where the size and velocity can be simultaneously extracted from particles [80, 81].

NIRS has been selected as preferred measurement method for PSD, leading to one single measurement method to follow critical quality attributes of final and intermediate products. The selected measurement method for the investigated wet granulation process in this thesis is NIRS in order to follow the API concentration, moisture content and PSD states along the continuous line: after calibration, NIRS as PAT tool can be applied in-line monitoring of process steps like blending (API blend uniformity), wet-granulation and drying (moisture content and PSD measurements), and tableting (API content uniformity) [79-85].

1.4.3 Deep learning

Deep learning provides advanced analytics tools to treat and analyze the great amount of data generated by continuous manufacturing. It fits into the Industry 4.0 framework of analyzing big data with many sensors and increase the process knowledge. The synergy between PAT and process data science could create a superior monitoring framework of the continuous manufacturing line. Deep learning can help for process monitoring, to create a reliable and robust process modeling and to better understand the process via analytics for process optimization [86-88].

1.4.4 Advanced process control

In pharmaceutical industry, the usual way of control is the use of PID controllers: they can also be implemented in pharmaceutical continuous manufacturing for local controls (e.g. valves, airflow regulation) but they are limited in capabilities. Continuous manufacturing is seeking for several approaches in order to tackle the automatized process control. Among these methods, model predictive control (MPC) is of high interest due to its ability to predict future process events and take control actions to keep the final product quality in range.

The main advantages of the MPC is its ability to systematically deal with multivariable dynamics, constraints and competing objectives [89]. MPC allows for operating the process close to the process constraints. It is the most widely used approach for the advanced control of complex dynamical systems. Model predictive control is a common technique used in the petrochemical industry [90, 91]. The pharmaceutical industries are not yet familiar with this real-time process control. Altough the continuous manufacturing is dealing with real-time challenge and the authorities are applying strict regulations to the final product quality, MPC could represent a potential key milestone in the adaptability and flexibility of the production mode in order to deliver drugs to patients even more efficiently.

Simulation studies [92, 93] were conducted and highlighted the advantages of MPC compared to PI-controllers. MPC allows the most flexible and straightforward design approach in combination with a high-performance control strategy. In fact, constraints can be easily considered in the optimization problem description by specifying minimum and maximum levels on variables; the design of the controller is straightforward once the mathematical models are established; and the tuning of the controller is intuitive [94].

1.5 Model predictive control (MPC)[2]

1.5.1 Operating mode

MPC is a class of control algorithms which relies on process models in order to make future plant outputs predictions while satisfying a set of constraints [95]. The aim of the MPC is to drive the predicted plant output as close as possible to the references, given by the operation team, which have clearly defined the purpose of the controller. The MPC design includes several items that guide the description for an accurate and efficient control function [94, 96]: the control objectives (e.g. improve the final product quality), the design level of operation mainly defined by normal operating ranges and classic disturbances, the constraints and the process interactions (e.g. key variables that drive some parameters). Figure 3 outlines the operating mode and gives a simplified version of the control algorithm. The operating mode [97-99] is as follows (see Figure 3 (a)):

- At $t=j$, the MPC solves an optimization control problem over a finite prediction horizon of N steps upfront in order to determine the control actions to be implemented over this horizon;
- At $t=j+1$, these determined control actions are implemented to the next time step only, while the whole optimization problem is solved again by the MPC and it results in new control actions;
- At $t=j+2$, the new control actions are applied, etc.

The iterative calculation of the optimal solution is based on measured input data and on predicted output data. Thus, the MPC is agile enough for the anticipation and the optimization of the process path and can implement control actions accordingly in order to avoid process events that could lead to fail the objectives.

The cost function (see Figure 3 (b)) is defined to calculate the deviation of the plant outputs from set points and system states as a weighted sum of errors. The optimization control problem is then solved by the MPC for a minimized cost function. In other words, the MPC is able to minimize the process divergence from the set points at each time step. The plant model simulates the output for a given control action and can be described by different mathematical models (e.g. mechanistic models or kinetic models), either for a single or for a group of operation unit(s) [94].

[2] Parts of this section have been previously published in Publication [22] and chapter 6, page 43.

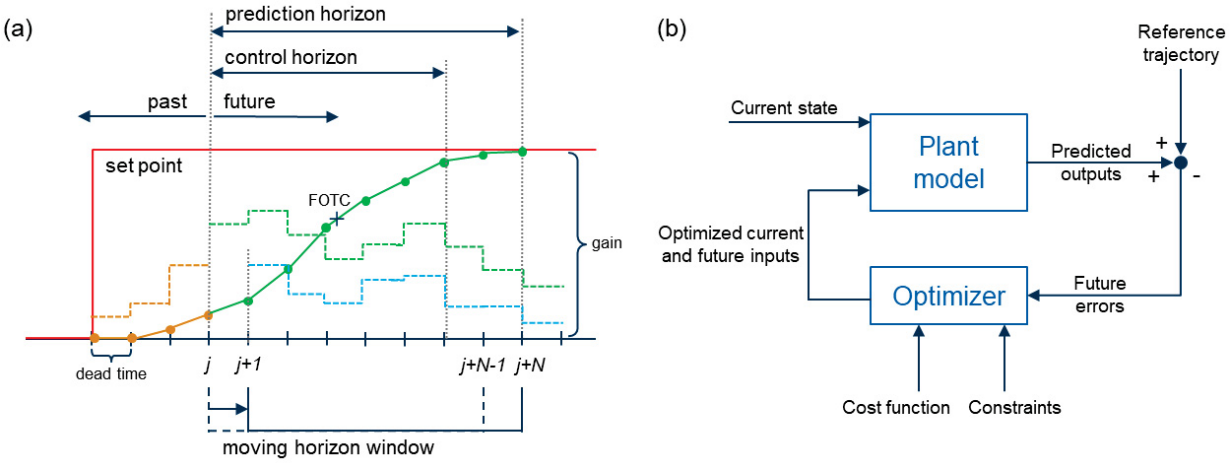

Figure 3: (a) Operating mode of the MPC and (b) simplified version of its control algorithm – figure adapted from [94, 97-99]. (a): The set point is changed (solid red). The optimized past inputs (dashed orange) influenced the past states (solid orange). The predicted output is displayed for time j (dashed green) and updated for time j+1 (dashed blue). The MPC is implementing only the first predicted output giving the current state (solid green) as the horizon window is moving.

1.5.2 Variables in MPC blocks

The current state of the process is reflected in the plant model of the MPC control algorithm and it is described by the process variables. The careful allocation of the process variables into the appropriate category (see Table 1) is determining for the successful implementation of the MPC with suitable design on a production line [94, 95].

Table 1: Categories for variables to be used in the MPC design.

Type of variable	Abbr.	Description
Controlled variable	CV	Variables to be controlled: the control objectives are defined by CVs set points and constraints. In the pharmaceutical world, the CVs are also known as the CQAs.
Manipulated variable	MV	Effective variables in manipulating the process: their conditions are modified to control the CVs. In the pharmaceutical world, MVs are equivalent to the CPPs.
Disturbance variable	DV	Uncontrolled measured variables, which have an impact on CVs to take into account.

Disturbance variables may be measured or unmeasured. Measured disturbances may be provided to the MPC block to warn it of the disturbance, so it can take immediate action and respond before the process is significantly disturbed. When unmeasured disturbances occur, the MPC block takes action to correct the symptoms of the disturbance, but only once the symptoms start to cause the process disturbance. In other words, unmeasured disturbances include all external effects that influence the process that are not measured, or where the measurement is too late to take effective action. The most likely DVs for a continuous wet granulation process are gathered in Table 2.

Table 2: Unmeasured disturbances in the continuous wet granulation process.

Unmeasured Disturbance	Notes
Change in feed powder properties	In the test process manual blends of powder are used and variability is eliminated. When part of a continuous cascade, this may be a significant source of unmeasured disturbance.
Change in liquid properties	Variability can be eliminated by use of pure solvent or by appropriate control of solvent properties.
Mechanical failure	Always a potential problem: control usually will be lost on the failure of process. The only failure control strategy that will be provided is the ability to manage poor solid feeder rate control. In this situation feed ratio control will take priority over total flow rate.
LOD measurement failure	This is not a true disturbance because only the control signal is affected and not the actual process but it may lead to wrong feedbacks. Nevertheless, this is probably the most likely source of disturbance to steady continuous operation. Signal validation and careful design for managing bad signals is essential.
All other disturbances	The MPC blocks will take action to correct any deviation from the specified operating point or allowed constraint envelope.

The CQAs (label claim, loss-on-drying, particle size distribution, etc) can be controlled by means of the manipulation of several process parameters, continuously measured on-line thanks to PAT tools and analyzed through appropriate ways to handle real-time data. In pharmaceutical continuous manufacturing, the control function is at a high level of complexity due to the number of process parameters it needs to control (e.g. solid feed rates, rotation speeds). Each of those process parameters can impact one or more CQAs of the final drug product [94]. This is why the implemented controller on the continuous line needs to be carefully designed in order to take control actions to either maintain the controlled parameters as close as possible to the reference values, mitigate undesirable events or discard OOS products.

1.5.3 Step tests and MPC models

Pharmaceutical development is seeking for a consistent high process performance leading to high final product quality. As described in the FDA guidance [9], the process flow can be characterized by the residence-time distribution by means of the mean residence time calculation (MRT). The MPC relies on process models in order to predict how variables could respond to changes. Relevant models can be developed for each CQA-CPP pair, where kinetic models can be used to describe the process behavior; they are defined by three parameters (see Figure 4):

- the dead time (DT), which corresponds to the difference between start time of the input step and start time of the observable response in the output;
- the rising time (first order time constant, FOTC), which corresponds to 63.2% of the trend area;

- the process gain (G), which corresponds to the change in input divided by the change in output. In other words, it expresses for example how far the measured controlled variable moves or reacts to a change in manipulated variable.

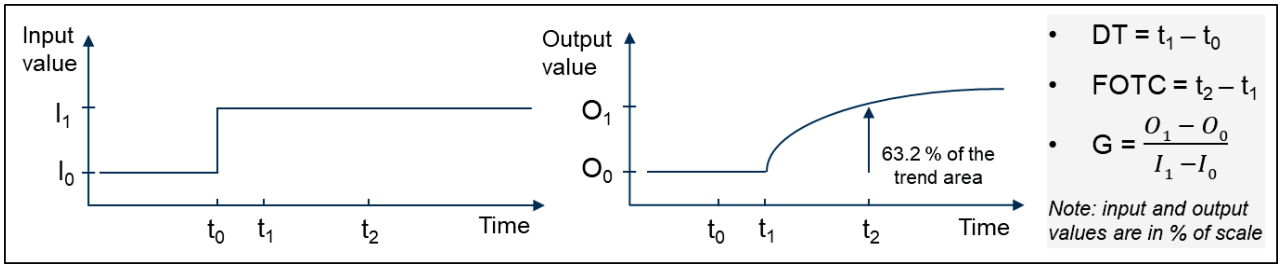

Figure 4: Illustration of a kinetic model with its gain and time constants.

In order to investigate the model parameters, a step test is conducted for each CQA-CPP pair; in other words, for each CV-MV pair. The step test is a technique among others which allows to identify the process dynamics by characterizing the process models. The step test is interesting because it allows to excite the system in the time-domain while the shape of the step allows to screen the whole spectrum of frequencies in the frequency domain; jump from one domain to another is available with the Fourier transform [100]. The step test is the most powerful tool to extract as much information in one shot.

The identification of accurate process models is made possible by a careful design of the step test (see Figure 5). The following recommendations should be followed:

- the step height should exceed at least three times the average noise of the data;
- the step length should be defined based on process knowledge and should be long enough to observe a reasonable plateau after the step;
- the step repetitions should be of three at least.

By this way, the three parameters describing the above mentioned kinetic models used in MPC predictions and control can be determined for each CV-MV pair.

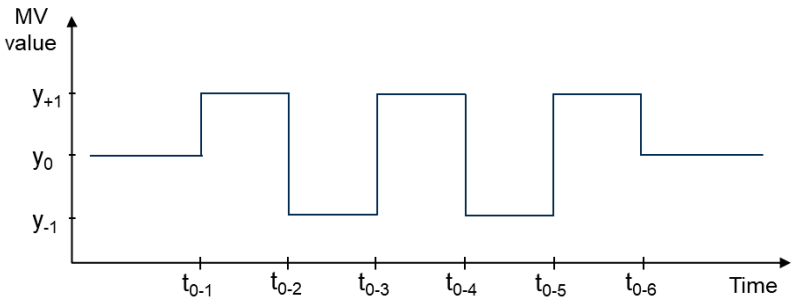

Figure 5: Step test design. The starting time of the step is defined as t_0; for the step number X, t_{0-X} is given.

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2 Aims of the thesis

The presented thesis aimed to investigate a continuous wet granulation line through process understanding and advanced process monitoring towards advanced process control.

- How to enhance the process monitoring?

With the investigated continuous manufacturing concept, the process units connected to each other from solid feeders to the dryer meaning the operators could be "blind" until the end of the processing units. One or several methods to verify the different critical quality attributes states could be necessary in order to provide safe drug product of highest quality: in-process tests are usual but are reliable on the sampling frequency. Process analytical tools could be provided; a fast and non-destructive method is preferred. Process data science can help in parallel. The thesis focused on the implementation of NIRS as PAT tool from a qualitative perspective to a quantitative monitoring of the process.

- How to characterize the process flow?

Last recommendations for continuous manufacturing from FDA and authorities considered the characterization of the process dynamics a critical step to achieve control strategy. Monitoring tools such as NIRS are able to tackle this issue by continuously recording the critical quality attributes. Deep learning techniques and residence time distributions could be potential key enablers for process flow characterization.

- How to control the process?

The FDA recognizes the challenge of continuous manufacturing to deal with real-time: process decisions should be done in real-time to achieve the best quality control possible, meaning efforts should be put on producing high quality drug products and out-of-specification products should be identified, sort out and wasted. Model predictive control (MPC) presents several benefits that could contribute to continuous manufacturing interests such as dealing with competing objectives and constraints. The chosen process control system should be adaptive to new drug products.

The cumulative manuscript is arranged with five publications, which are presented to respond each of the above mentioned questions. Qualitative monitoring of the continuous wet granulation process is presented with the introduction of NIRS as PAT tool. Then, deep learning techniques have been applied for quantitative prediction of the plant outputs. Residence time distributions have been computed for dynamic prediction of time characteristics of the investigated process with the possibility to divert OOS products. Finally, a review of the literature presented the MPC as an interesting tool to achieve process control together with the last publication, demonstrating how to design and implement such a control tool on a continuous wet granulation line from solid feeders to the dryer.

The following chapters contain the results of the dissertation which have been published/submitted in international journals. Each chapter contains a short introduction and summary of the work together with the assignments of tasks of the authors. Figures, tables and schemes do not follow the numbering of the main text, but the numbering of the publication itself. Each publication has its own reference list.

3 Continuous manufacturing process monitoring of pharmaceutical solid dosage form: A case study

Yves Roggo[1], Victoria Pauli[1], Morgane Jelsch[1], Laurent Pellegatti[1], Frantz Elbaz[1], Simon Ensslin[1], Peter Kleinebudde[2], Markus Krumme[1]

[1] Novartis Pharma AG, Continuous Manufacturing (CM) Unit, CH-4002, Basel, Switzerland

[2] Institute of Pharmaceutics and Biopharmaceutics, Heinrich Heine University, Düsseldorf, Germany

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DOI: https://doi.org/10.1016/j.jpba.2019.112971

3.1 Pretext

This chapter is aimed to introduce process analytical tools (PAT) via near-infrared spectroscopy (NIRS) sensors, newly implemented on the line for process monitoring. It also investigates the impact of the three main factors of wet granulation on the tablet quality with a design of experiments (DoE), followed with in-process control (IPC) tests, NIRS as well as univariate and multivariate analysis of the process parameters. One step ahead process understanding, it introduces statistical process control (SPC), defined as the use of statistical techniques to control a process in order to monitor process behavior.

This publication represents the starting point of the process monitoring presented in this thesis for a wet granulation line in pharmaceutical continuous manufacturing. NIRS as PAT tool allows here a qualitative process monitoring of the continuous production line.

3.2 Evaluation of the authorship

Author's contribution to the publication:

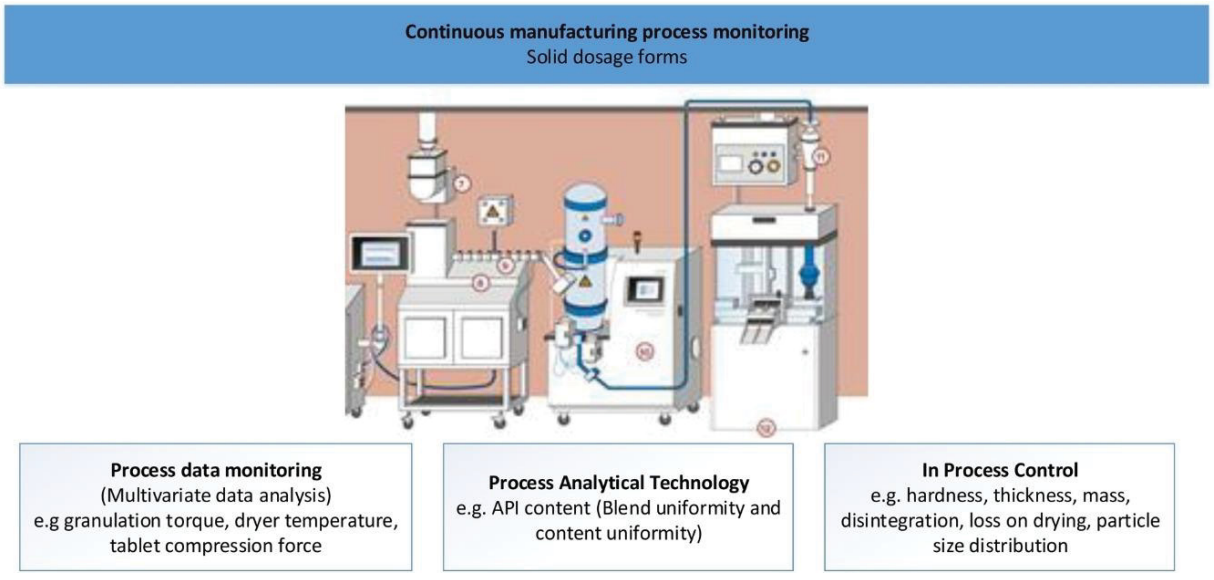
- Drew NIR models
- Performed univariate data analysis
- Performed statistical analysis

Overall contribution of the author is estimated at 15% of this publication.

3.3 Abstract

Continuous Manufacturing (CM) of pharmaceutical drug products is a rather new approach within the pharmaceutical industry. In the presented paper, a GMP continuous wet granulation line used for clinical production of solid dosage forms was investigated with a thorough monitoring strategy regarding process performance and robustness. The line was composed of the subsequent continuous unit operations feeding – twin-screw wet-granulation – fluid-bed drying – sieving and tableting; the formulation of a new pharmaceutical entity in development was selected for this study. In detail, a Design of Experiments (DoE) was used to evaluate the impact of the three main factors (amount of water, filling rate, and shear force in twin-screw granulator) on the tablet quality. The process was monitored via in-process control (IPC) tests (e.g. weight, hardness, disintegration, and loss-on-drying), Process Analytical Technologies (PAT), and through the analysis of the process parameters (multivariate process control). The tested formulation was very robust to the large process variation of the DoE: all IPC results were in specification, the PAT probes provided stable results for the content uniformity and no critical variations can be detected in the process parameters. An adequate monitoring strategy was presented and the robustness of the process with one formulation has been demonstrated. In summary, this continuous process in combination with smart formulation development allows the robust production of constant quality tablets. The synergy between PAT, process data science and IPC creates an adequate monitoring framework of the continuous manufacturing line.

3.4 Graphical abstract



4 Deep learning for continuous manufacturing of pharmaceutical solid dosage form

Yves Roggo[1], Morgane Jelsch[1], Philipp Heger[1], Simon Ensslin[1], Markus Krumme[1]

[1]Novartis Pharma AG, Continuous Manufacturing Unit, 4002 Basel, Switzerland.

European Journal of Pharmaceutics and Biopharmaceutics, 2020, 153: 95-105.

DOI: https://doi.org/10.1016/j.ejpb.2020.06.002

4.1 Pretext

In this chapter, the same GMP continuous wet granulation line for production of solid dosage forms than in the last chapter (see section 3, page 39 for further details) is investigated with the aim of deep process understanding and increased process monitoring.

Several critical process parameters were selected based on risk analysis and evaluated via step tests in order to probe the process and to characterize the impact on quality attributes. NIRS models were drawn for API concentration, LOD and PSD in order to perform a multivariate process analysis. The investigated deep learning techniques allowed the development of advanced quantitative prediction method for the investigated critical quality attributes.

4.2 Evaluation of the authorship

Author's contribution to the publication:

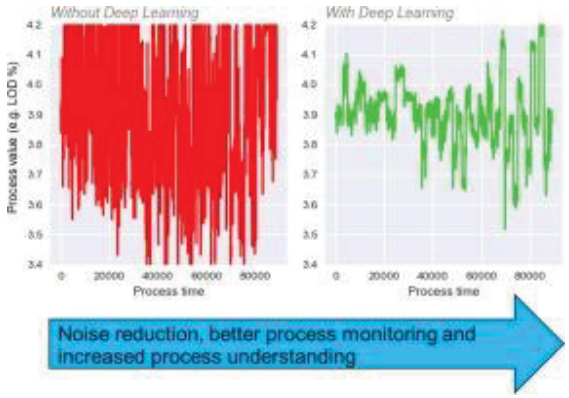
- Designed, planned, performed and evaluated the required step tests
- Interpreted data and results
- Performed statistical analysis
- Prepared GMP environment related documents for production (process check-lists, API and excipients purchase orders, protocols)

Overall contribution of the author is estimated at 45% of this publication.

4.3 Abstract

Continuous Manufacturing (CM) of pharmaceutical drug products is a new approach within the pharmaceutical industry. In the presented paper, a GMP continuous wet granulation line for production of solid dosage forms was investigated. The line was composed of the subsequent continuous unit: operations feeding – twin-screw wet-granulation – fluid-bed drying – sieving and tableting. The formulation of a commercial entity was selected for this study. Several critical process parameters were evaluated in order to probe the process and to characterize the impact on quality attributes. Seven critical process parameters have been selected after a risk analysis: API and excipient mass flows of the two feeders, liquid feed rate and rotation speed of the extruder and rotation speed, temperature and airflow of the dryer. Eight quality attributes were controlled in real time by Process Analytical Technologies (PAT): API content after blender, after dryer, in tablet press feed frame and of tablet, LOD after dryer and PSD after dryer (three PSD parameters: x10 x50 x90). The process parameter values were changed during production in order to detect the impact on the quality of the final product. The deep learning techniques have been used in order to predict the quality attribute (output) with the process parameters (input). The use of deep learning reduces the noise and simplify the data interpretation for a better process understanding. After optimization, three hidden layers' neural network were selected with 6 hidden neurons. The activation function ReLU (Rectified Linear Unit) and the ADAM optimizer were used with 2500 epochs (number of learning cycle). API contents, PSD values and LOD values were estimated with an error of calibration lower than 10%. The level of error allows an adequate process monitoring by DNN and we have proven that the main critical process parameters can be identified at a higher level of process understanding. The synergy between PAT and process data science creates a superior monitoring framework of the continuous manufacturing line and increase the knowledge of this innovative production line and the products that it makes.

4.4 Graphical abstract



5 Automatic system dynamics characterization of a pharmaceutical continuous production line

Morgane Jelsch[1], Yves Roggo[1], Ahmad Mohamad[1], Peter Kleinebudde[2], Markus Krumme[1]

[1] Novartis Pharma AG, Continuous Manufacturing (CM) Unit, CH-4002 Basel, Switzerland.

[2] Heinrich Heine University, Universitätsstraße 1, 40225 Düsseldorf, Germany.

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DOI: https://doi.org/10.1016/j.ejpb.2022.09.010

5.1 Pretext

This chapter is aimed to address the characterization of the process dynamics. The interest of this publication is not only to understand and monitor the wet granulation process but also to define and monitor the process time characteristics. It is one step ahead in the direction of process control. By assessing the residence time distribution (RTD) along the process line, it is possible to characterize the process flow. Steps in API concentration have been done in order to easily follow the propagation of the state along the process (as a tracer; without any additional dye) and NIRS as PAT tool has been used to monitor the process. An automatic method for RTD calculation is suggested, allowing an accurate process dynamics assessment to be further used for control strategy and diversion strategy.

5.2 Evaluation of the authorship

Author's contribution to the publication:

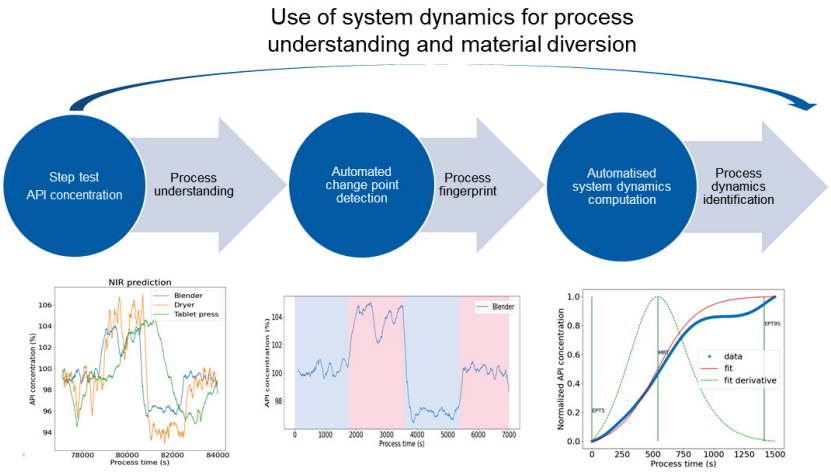
- Designed, planned, performed and evaluated the required step tests
- Calculated RTD characteristics "manually"
- Interpreted data and results
- Developed the automatic RTD method in collaboration with Yves
- Wrote for paper publication
- Prepared GMP environment related documents for production (process check-lists, API and excipients purchase orders, protocols)

Overall contribution of the author is estimated at 60% of this publication.

5.3 Abstract

Continuous Manufacturing (CM) of drug products is a new approach in the pharmaceutical industry. In the presented paper, a GMP continuous wet granulation line for production of solid oral dosage forms was investigated in order to assess the system dynamics of the line and to define the best control and diversion strategy. The following steps were involved in the continuous process: dosing / feeding, blending, twin-screw wet granulation, fluid-bed drying, sieving and tableting. Two drug products with two different drug substances were compared during this study: one drug substance as model drug compound and one formulation of a currently evaluated commercial drug product. Several step tests in API concentration were performed in order to characterize the process flow and assess the process dynamics. API content was monitored in real time by Process Analytical Technologies (PAT) thanks to three Near Infrared (NIR) probes located along the process and measuring the API content after blender, after dryer and in the tablet press feed frame. The process parameter values were changed during production in order to detect the impact on the quality of the final product. An automatic residence time distribution (RTD) computation method has been developed in order automate the RTD calculation on the basis of process data to further define and monitor the system dynamics with the final aim of out of specification material diversion during the continuous production. The RTD has been seen as a process fingerprint: a change in the RTD values implies a change in the process.

5.4 Graphical abstract



6 Model predictive control in pharmaceutical continuous manufacturing: A review from a user's perspective

Morgane Jelsch[1], Yves Roggo[1], Peter Kleinebudde[2], Markus Krumme[1]

[1] Novartis Pharma AG, Basel, Switzerland

[2] Heinrich Heine University, Düsseldorf, Germany

European Journal of Pharmaceutics and Biopharmaceutics, 2021, 159: 137-142.

DOI: https://doi.org/10.1016/j.ejpb.2021.01.003

6.1 Pretext

This chapter is the starting point for advanced process control with Model Predictive Control (MPC). With the growing understanding of process dynamics and the appropriate control strategy, continuous manufacturing defines the framework for Quality-by-Design, introducing next Quality-by-Control concept, which can be reached by soft sensors such as MPC. The publication highlights the numerous benefits of process control via MPC compared to usual PID controllers, and it gives a literature review of the MPC development in the pharmaceutical continuous manufacturing world. It can be seen as situational analysis of what is suggested by academies and industries. The paper shows the gaps in MPC development and MPC implementation in pharmaceutical continuous manufacturing.

6.2 Evaluation of the authorship

Author's contribution to the publication:

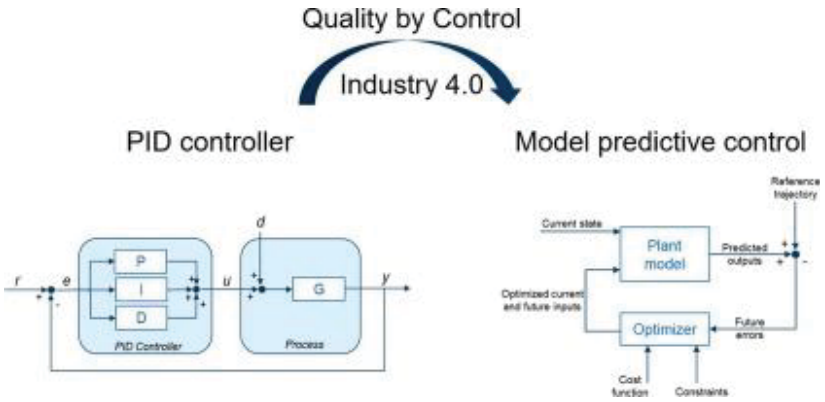
- Understanding of the MPC topic
- Review of literature
- Research and redaction

Overall contribution of the author is estimated at 80% of this publication.

6.3 Abstract

Pharmaceutical continuous manufacturing is considered as an emerging technology by the regulatory agencies, which have defined a framework guided by an effective quality risk management. With the understanding of process dynamics and the appropriate control strategy, pharmaceutical continuous manufacturing is able to tackle the Quality-by-Design paradigm that paves the way to the future smart manufacturing described by Quality-by-Control. The introduction of soft sensors seems to be a helpful tool to reach smart manufacturing. In fact, soft sensors have the ability to keep the quality attributes of the final drug product as close as possible to their references set by regulatory agencies and to mitigate the undesired events by potentially discard out of specification products. Within this review, challenges related to implementing these technologies are discussed. Then, automation control strategies for pharmaceutical continuous manufacturing are presented and discussed: current control tools such as the proportional integral derivative controllers are compared to advanced control techniques like model predictive control, which holds promise to be an advanced automation concept for pharmaceutical continuous manufacturing. Finally, industrial applications of model predictive control in pharmaceutical continuous manufacturing are outlined. Simulations studies as well as real implementation on pharmaceutical plant are gathered from the control of one single operation unit such as the tablet press to the control of a full direct compaction line. Model predictive control is a key to enable the industrial revolution or Industry 4.0.

6.4 Graphical abstract



7 Advanced process automation of a pharmaceutical continuous wet granulation line: Perspectives on the application of a model predictive control from solid feeders to dryer

Morgane Jelsch[a], Yves Roggo[a], Mark Brewer[b], Zsolt-Adam Géczi[a,b], Philipp Heger[a], Peter Kleinebudde[c], Markus Krumme[a]

[a] Novartis Pharma AG, Basel

[b] Emerson Automation Solutions

[c] Heinrich Heine University, Düsseldorf

Powder Technology, 2023: 118936.

DOI: https://doi.org/10.1016/j.powtec.2023.118936

7.1 Pretext

This chapter presents the development of an advanced process control method with model predictive control (MPC). As a new tool being introduced on the investigated continuous wet granulation line, the control objectives have been defined and the MPC has been designed and set-up. The whole MPC structure had to be implemented on the live system.

Through several step tests and two different drug products, deep process understanding and enhanced process dynamics were investigated to model the process and predict plant outputs in real-time. The MPC control system is able to keep the critical quality attributes within pre-defined ranges over time. Some process models are related to the drug product.

7.2 Evaluation of the authorship

Author's contribution to the publication:

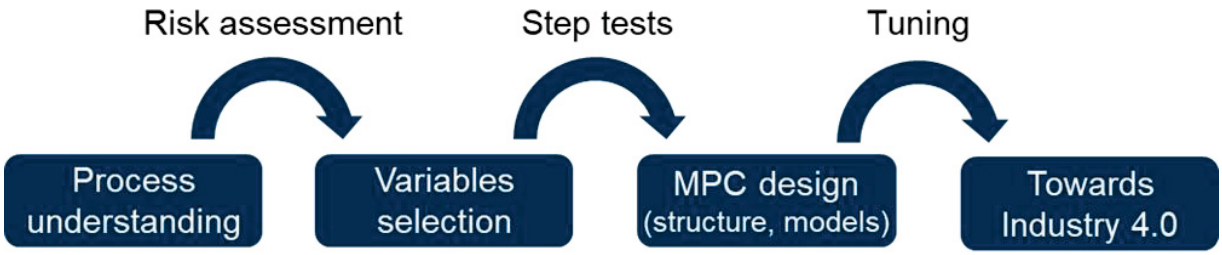
- Deeply involved in the MPC design and MPC setup strategies
- Designed, planned, performed and evaluated the required step tests
- Calculated RTD characteristics
- Drew MPC models, discussed with team
- Designed, planned, performed and evaluated the MPC performance tests
- On-the-fly evaluation of the MPC performance for tuning during production
- Performed the reference analytics (LOD, PSD) and asked for support in HPLC
- Summarized and wrap-up data and decisions for paper publication
- Prepared GMP environment related documents for production (process check-lists, API and excipients purchase orders, protocols)

Overall contribution of the author is estimated at 80% of this publication.

7.3 Abstract

Pharmaceutical continuous manufacturing provides the appropriate tools (e.g. the understanding of process dynamics and appropriate and adaptable control strategy) in order to deal with Quality-by-Design expectations and even to the future smart manufacturing described by Quality-by-Control. Those tools form part of the given framework of the regulatory agencies led by an effective quality risk management. Soft sensors and control algorithms such as model predictive control are stepping stones for more agile processes and increased robustness by keeping the quality attributes of the final drug product in their acceptable ranges and by mitigating undesired events. The implementation of a model predictive control (MPC) system on a pharmaceutical continuous manufacturing plant for the wet granulation process is described. The control objectives and strategy are presented as well as the selected variables, the process dynamics identification, the MPC performance and its specific tuning where a commercial software has been used, setting the framework of this study. MPCs have been applied successfully on two pharmaceutical drug products (Diclofenac and Paracetamol): an accurate control of the API content and of the LOD was achieved in order to produce a constant quality of tablets on both drug products. In addition, some of the process parameters have been identified as mandatory to be step tested for each change of drug product, leading to a simplified MPC implementation.

7.4 Graphical abstract



8 Discussion and outlook

The following chapters aimed to answer the aims of the thesis, one by one.

8.1 How to enhance the process monitoring?

The continuous wet granulation process has been investigated to find new ways for process monitoring [101]. By means of design of experiments (DoE), the focus has been put on the following granulation parameters: amount of water, filling rate, and shear force in twin-screw granulator. The intermediates (i.e. dried granules) and final tablet quality attributes have been investigated.

The usual way to monitor drug product quality was to perform in process control (IPC) tests, either at the end of the dryer collecting dried granules for loss-on-drying (LOD) or particle size distribution (PSD) measurements, or at the end of the processing operations in order to test final critical quality attributes of tablets (e.g. weight, thickness, diameter and hardness).

The feed rate of the twin-screw granulator has been investigated as main factor influencing the filling rate in the granulator; the torque of the twin-screw granulator allows to follow the changes in shear force during granulation; respective inlet and outlet humidity in the dryer were reflecting the amount of water. In general, IPC results were in specification and no critical variations could be detected in the process parameters.

Several process data analyses of the process parameters have been performed during this study giving enhanced process understanding: univariate and multivariate analyses of process data, with principal component analysis (PCA) allowed to investigate the process monitoring strategy with regard to process performance and robustness for stable drug product quality. With this increased process knowledge, correlations have been drawn between process parameters and quality attributes leading to the possibility of monitoring the drug product quality via univariate and multivariate analyses of process parameters.

An extra layer to process monitoring is the introduction of PAT tools such as NIRS. Three NIR probes have been implemented in-line on the continuous wet granulation line in order to analyze dried granules and tablets in three locations of the continuous line for the respective monitoring of granules after the fluid-bed dryer, of sieved granules in the tablet press feed frame and of tablet content uniformity at the end of the tablet press. The results of this first implementation were satisfactory and encouraging.

A process monitoring strategy has been proposed and focused on potential critical process parameters for granulation, which have been selected based on previous risk assessment [44]. Three ways to monitor the process have been studied: IPC tests, PAT measurements and univariate and multivariate analyses as process data science in order to introduce a potential statistical process control (SPC). Enhanced process understanding has been created with the analysis of the DoE concerning PSD and wet granulation process parameters. The torque of the twin-screw granulator is highly correlated with the PSD and can be followed for PSD monitoring. A more holistic

approach would have been appreciated, to not only focus on granulation but also to take into considerations blending, drying and tableting process parameters.

DoE is a structured approach for conducting experiments, it can help to find the most suitable parameters in agreement with the required and desired objectives during product and process development. The design space is defined by the critical process parameters and critical quality attributes of intermediates and final drug product. DoE can be used for the implementation of Quality-by-Design where product and process understanding facilitates final product quality assurance [102].

The process data science provides a framework for qualitative monitoring of the continuous wet granulation line. The PAT probes provided stable results for the content uniformity and NIR is able to further provide quantitative monitoring of the continuous wet granulation process.

In fact, quantitative NIR models can be developed for process data in order to predict critical quality attributes. By means of a DoE and partial least square (PLS) as process data science, robust NIR method gave acceptable prediction performance against material, instrument and process variation [103].

The second study presented in the dissertation investigated the quantitative process monitoring based on NIRS and deep learning techniques [104]. The test design took into consideration the critical process parameters of the whole continuous wet granulation process from solid feeders to the fluidized-bed dryer (FBD). The tablet press process parameters were out of scope. Four NIR probes recorded the API content along the line: after blender, after FBD, in the tablet press feed frame and at the end of the tablet press. LOD and PSD were recorded by NIRS after the dryer only.

NIR models are sensitive to the formulation and drug product [105]. As the formulation have been updated for this study, new NIR models have been built with the production run data.

Step tests of the critical process parameters have been performed with the following criteria: the step test have been designed in a way the operators can see a durable change in the linked critical quality attributes. The developed method with deep learning techniques allowed to define the relationships between CQAs and CPPs leading to enhanced process understanding for the continuous wet granulation process. It helped for data interpretation as well with noise reduction in the dataset. Correlations between CPPs and CQAs result of the deep learning method.

Artificial neural networks (ANN) have been applied on the PAT data. The first set of data has been used to calibrate the developed deep learning technique while the second set of data has been used to validate the deep learning technique. The ANN models were conclusive for all API content records, for LOD and for PSD. The challenge in this method was to optimize the deep learning technique. Once it has been built it is reusable on an infinite amount of dataset.

This multivariate advanced prediction method is quantitative. Process monitoring by deep neural networks is possible. It paves the way to more digitalization with quantitative prediction of plant outputs.

8.2 How to characterize the process flow?

NIRS seems to be a suitable monitoring tool for pharmaceutical continuous manufacturing as it is a fast, non-destructive and adaptive PAT tool. With a high measurement frequency, NIRS is able to continuously record the critical quality attributes of intermediated and final drug product.

According to FDA [9], one of the goals for continuous manufacturing is to apply a control strategy based, among others, on input materials control by means of a proper flow behavior characterization. In other words, continuous manufacturing needs the identification of the process dynamics.

Step tests in API concentration have been performed on a continuous wet granulation line in order to assess the dynamics of the process [106]. The step test consists in changing a critical process parameter set point: it forms a step and not a ramp-up, where the operators would lose precious information about process dynamics. The step test should be accurately designed in step amplitude, step sign and step sequence. Several step tests can be suggested.

The study showed that NIRS as PAT tool for real-time process monitoring was able to detect small API concentration change (+/- 7,5 %) as well as bigger changes (+/- 20 %). Two drug products were compared. API concentration has been used as a tracer. NIRS is a suitable tool to observe the propagation of events along the process with four observation points: after the blender, after the fluidized bed dryer, in the tablet press feed frame and after the tablet press. From visual observations, it is easy to see time lags between those observation points.

The suggested method aimed to characterize those time lags with residence time distribution (RTD). With the increased number of step tests needed in continuous manufacturing (flow characterization and process modeling), it is suggested to automatize the RTD computation method. RTD is given by metrics defining the process dynamics and it can be determined by means of curve fitting on the filtered data.

The developed method starts with a significance test for steps in order to discriminate real process steps from artefacts. Then, the signal is preprocessed by means of wavelet filter. A change point detection method is applied and RTD is computed. Process dynamics are described by RTD, given by mean residence time (MRT) and event propagation times at 5% and 95% of the step change (i.e. EPT5 and EPT95).

The understanding of the RTD enables to develop the diversion and sampling strategies by tracking the material from the origin of disturbance to the points of diversion. RTD represents the fingerprint of the process. The automatized computation method has been developed in order to improve the process understanding and to propose an innovative monitoring strategy of a continuous manufacturing line.

In another study [107], mean residence time computation has been used to select tracers with different material properties in powder systems. The highlighted challenge when using additional tracer to follow the propagation of a state is to select one with very close material properties to the produced formulation, otherwise differences in travel time can be seen between tracer and bulk material.

8.3 How to control the process?

Continuous manufacturing in pharmaceutical applications deals with high quality standards for the produced drug products, compared to oil and gas industries where the ultimate goal would be to set the most profitable and cost-effective process parameters.

Per definition, continuous manufacturing generates a lot a data that should be evaluated in real-time to make process decisions. It would require an automated system, whose validation would be particularly critical according to FDA guidance [9].

A literature review [94] highlighted the benefits of advanced process control techniques such as model predictive control (MPC) compared to usual PID (proportional integral derivative) controllers. The latter is more suitable to local control such as the control of valves while the first one is really suitable to the optimization of a control issue with several inputs and outputs, competing objectives and constraints. It applies a systematic approach of resolving the optimization issue at each time step (e.g. it could be every 1 second, if it is set so) while satisfying a set of constraints and applying the required control actions. Accurate process models are required for effective MPC actions. Such a control tool would move the pharmaceutical continuous manufacturing towards Quality-by-Control (QbC).

The last study presented in the dissertation aimed to develop the MPC on a continuous wet granulation process [108]. Control objectives were defined to run the line at a specified production rate, whilst keeping the product assay, moisture content and particle size distribution within acceptable limits. The MPC variables have been carefully selected and are distributed in three categories (i.e. manipulated variables, controlled variables and disturbance variables). Several step tests were done to investigate process modeling, based on RTD computation.

In a previous study [106], it has been proposed to define RTD by three characteristics: mean residence time (MRT) and event propagation times at 5% and 95% of the trend (respectively EPT5 and EPT95). This concept has been re-used and applied to process modeling. Usually, MPC models deal with three characteristics: dead time, first order time constant and gain. In the MPC implementation study [108], it has been proposed that dead time would be associated with EPT5 and first order time constant (which corresponds to 63,2% of the trend area) would be roughly estimated as MRT (which corresponds to 50% of the trend area). This difference in model characteristics may affect the MPC control actions for sure but the assumption was that the MPC will be able to deal with this. Several performance tests were done and were always conclusive, except for PSD models.

Unfortunately, it was not possible to draw sufficiently strong model between PSD and its linked critical process parameters. This is mainly due to poor measurement method for PSD. In fact, measuring PSD via NIRS was part of a concept for integrated PAT tool: NIR probes would give several information with one single measurement. Even if it is possible to see differences in spectra while NIR models are prepared in laboratory (i.e. several samples of granules are prepared with varied API content, LOD and PSD), it becomes more difficult to grasp the PSD information from the continuous process line. The hypothesis is to say that with semi-continuous flow at the end of the fluidized bed dryer (due to the ejection of one rotating chamber after the other), dried granules

sit for a while in front of the NIR probe (which does not harm the LOD or API content measurement) and it results in having only a small portion of the produced granules being measured. In other words, the probability to see a representative sample is low at this point for the measurement of PSD of dried unsieved granules.

The measurement method for PSD should be improved before taking any additional effort in modeling the PSD behavior.

Other studies evaluated the implementation of MPC in a rotary tablet press of a continuous direct compaction process [63, 109] for example, or in an end-to-end continuous manufacturing pilot plant (from chemical synthesis to melt extrusion and tableting) [110].

Our study compared the process models of two different drug products (i.e. Diclofenac and Paracetamol) and pointed out that some process models were unchanged leading to a simplified MPC implementation. In fact, for a new product, it may be possible to re-assess only the process models that are dependent to the formulation or drug product.

With regards to the control perspective, it has been highlighted that the ratio control of solid feeds worked really well and the process models are transferable from material to material. The ratio control of the liquid feed with regards to the sum of the two solid feeds also worked well given a satisfactory control of L/S ratio. The particle size distribution as one of the responses for the defined optimization objective of the MPC controller seemed to be overall insensitive within the tested range of wet granulator rotation speed. The control perspective seemed compromised. However, an insensitive process is not necessarily a disadvantage: it can be an asset for the robustness of process as no matter how deep the involved parameters would change, the PSD would still remain the same. The blender seemed also robust in itself, when the blender rotation speed is set above a critical rotation speed.

These two insensitivities were represented by very low gains in related process models. The intrinsic uncertainty of insensitive processes was reflected in data by some noise. The recommendation for cases like that would be to not control the process in a closed-loop manner but rather run it with no control loop or open-loop.

On the other hand, the control of the investigated process through the LOD response depicted a nice example for a sensitive process.

The MPC controller could obviously keep the process stable even though the disturbance was significant. The process models parameters seemed to be sensitive to material. The biggest asset is that they can be easily tuned per product in the late stage development in one final run before drug product pre-validation.

In addition, the LOD control action is a time-variable balanced superposition of three control actions: air flow, air temperature and rotation speed of the dryer. No other control strategy than MPC can support such a control challenge with finding the optimal trajectory in balancing the three manipulated variables over time and shifting the respective contributions to the overall control action.

To conclude, the overall strategy for the implementation of the MPC on a pharmaceutical continuous manufacturing line would be the following:

1. Careful design of the MPC structure by properly setting the control objectives, the variables, the design level of operation and the constraints, limits and ranges;
2. Assessment of the process dynamics by stepping the selected variables and MPC models generation for the selected CQA–CPP pair by identifying real world data;
3. Validation and tuning of the above mentioned MPC models either by simulation or by real test on the plant;
4. MPC implementation on the plant and MPC assessment of the product-dependency of this control system with different products.

Pharmaceutical continuous manufacturing is ready to tackle the Industry 4.0 challenges with embedded NIRS as innovative process analytical technology, process data science, artificial intelligence in real-time, advanced process understanding (e.g. residence time model) and state of the art automation (e.g. MPC controller).

8.4 References

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9 Summary

Pharmaceutical industries are seeking for new production ways with the general objective of always improving the quality standards of drug products to be safer and potentially more effective for the patient. In that direction, regulatory authorities went through several steps in FDA guidances for industry or ICH harmonized guidelines: pharmaceutical development was encouraged and a framework for the management of quality risks and quality systems has been suggested. In parallel, PAT has been introduced as innovative tools for quality assurance. In addition, the growing interest for ecological issues foster "green" manufacturing; industries such as pharmaceutical manufacturing were seeking for more eco-friendly manufacturing with reduced footprint, but also flexible and agile manufacturing.

Continuous manufacturing has been investigated by academies and pharmaceutical industries as it may provide the means to meet that demand. Flexible, agile, with reduced footprint and improved engineering systems, it may provide real-time quality assurance. The presented publications in this thesis aimed to provide meaningful data for continuous process monitoring and continuous process control.

The goal was to set up suitable and adaptive tools for process monitoring in pharmaceutical continuous manufacturing in order to better understand the process. In-process control (IPC) tests were used (e.g. crushing force, weight, thickness, diameter of produced tablets) with the challenge of the sampling strategy: frequency, amount, potential destructive method applied for tablets in particular with crushing force test of tablets. Univariate and multivariate process parameters analyses introduced process data science. NIRS as new PAT tool was introduced on a continuous wet granulation and it has been demonstrated that it is a suitable method for qualitative process monitoring.

Globally with IPC tests, it was possible to follow the drug product quality once being compressed into tablets (possible withdrawal of product could have been done a step before *i.e.* at the end of the dryer with poor additional value). With increased process knowledge, relationships between process parameters and quality attributes have been investigated leading to the possibility of monitoring the drug product quality via critical process parameters. An extra layer to process monitoring is the introduction of PAT tools such as NIRS. NIRS as a fast and non-destructive analytical method was particularly suitable to continuous manufacturing with the possibility to implement several probes along the process for monitoring of critical quality attributes of intermediates and final drug product.

Deep learning techniques can be applied in parallel of PAT tools to monitor the process but also to increase process knowledge and process understanding by clearly assessing the relationships, links and correlations between critical process parameters and critical quality attributes. It paves the way to process modeling for quantitative predictions about plant outputs.

Additional information can be provided by the evaluation of the propagation of a state. By introducing steps in API content, operators can follow the propagation of the API content along the continuous wet granulation line. It then plays the role of a tracer and its propagation can be

observed via NIR probes. Residence time distribution (RTD) can be calculated based on NIR data. Process modeling is now possible in the time dimension, assessing the process dynamics of the continuous wet granulation line. RTD information allows to characterize the process flow in order to further apply a control strategy, in agreement with the regulatory authorities.

A literature review about model predictive control (MPC) highlighted benefits and challenges of this method for applied control strategy. It showed the gaps in literature, in particular the specific lack of study for pharmaceutical continuous wet granulation line from solid feeders to dryer. Some examples of simulated and/or implemented MPC have been given.

A proper control strategy has been designed for the investigated wet granulation line with MPC as control framework. Control strategy starts with the proper definition of the control objectives, then control variables should be selected carefully in such a design. Deeper process modeling has been done with step tests for all assessed critical process parameters and RTD computation in order to build accurate process models. The MPC structure has been tested for its control performance with two drug products: Diclofenac and Paracetamol. This study allowed to compare the process models and some differences were highlighted where process models resulted in being dependent of the formulation or drug product. It leads to a simplified version of the MPC implementation, where some process models are pre-defined and some others need a re-assessment as soon as the formulation or drug product changes.

It has been shown how a multivariate process of unknown sensitivity matrix can be characterized by the sequential step tests in a simple and comprehensive integral way and how this process can be driven through a meaningful stabilization against unplanned disturbances, that would translate into non-conforming material if uncontrolled.

10 List of original publications

1. Yves Roggo, Victoria Pauli, Morgane Jelsch, Laurent Pellegatti, Frantz Elbaz, Simon Ensslin, Peter Kleinebudde, Markus Krumme

   Continuous manufacturing process monitoring of pharmaceutical solid dosage form: A case study

   Journal of Pharmaceutical and Biomedical Analysis, 2020, 179: 112971. (https://doi.org/10.1016/j.jpba.2019.112971)

2. Yves Roggo, Morgane Jelsch, Philipp Heger, Simon Ensslin, Markus Krumme

   Deep learning for continuous manufacturing of pharmaceutical solid dosage form

   European Journal of Pharmaceutics and Biopharmaceutics, 2020, 153: 95-105. (https://doi.org/10.1016/j.ejpb.2020.06.002)

3. Morgane Jelsch, Yves Roggo, Peter Kleinebudde, Markus Krumme

   Model predictive control in pharmaceutical continuous manufacturing: A review from a user's perspective

   European Journal of Pharmaceutics and Biopharmaceutics, 2021, 159: 137-142. (https://doi.org/10.1016/j.ejpb.2021.01.003)

4. Morgane Jelsch, Yves Roggo, Ahmad Mohamad, Peter Kleinebudde, Markus Krumme

   Automatic system dynamics characterization of a pharmaceutical continuous production line

   European Journal of Pharmaceutics and Biopharmaceutics, 2022, 180: 137-148. (https://doi.org/10.1016/j.ejpb.2022.09.010)

5. Morgane Jelsch, Yves Roggo, Mark Brewer, Zsolt-Adam Géczi, Philipp Heger, Peter Kleinebudde, Markus Krumme

   Advanced process automation of a pharmaceutical continuous wet granulation line: Perspectives on the application of a model predictive control from solid feeders to dryer

   Powder Technology, 2023, 429: 118936. (https://doi.org/10.1016/j.powtec.2023.118936)

11 Conference contribution

1. Morgane Jelsch, Yves Roggo,

   Dynamic study of loss-on-drying on a continuous wet granulation line

   12th World meeting APV Vienna, March 2021

2. Yves Roggo, Laurent Pellegatti, Morgane Jelsch, Simon Ensslin, Markus Krumme

   Near infrared spectroscopy and chemometrics for pharmaceutical continuous manufacturing

   Chimiometrie 2020, Liège, Belgique, January 2020

12 Erklärung

Hiermit erkläre ich gemäss §5 Absatz 1 der Promotionsordnung der Mathematisch-Naturwissenschaftlichen Fakultät der Heinrich-Heine-Universität Düsseldorf des Eides Statt, dass die Dissertation von mir selbständig und ohne unzulässige fremde Hilfe unter Beachtung der «Grundsätze zur Sicherung guter wissenschaflticher Praxis an der Heinrich-Heine-Universität Düsseldorf» erstellt worden ist und dass ich diese in der vorgelegten oder in änhlicher Form noch bei keiner anderen Institution eingereicht habe.

_____

Ort, Datum und Unterschrift

Morgane Jelsch

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