Process Parameter Analysis and process understanding — Some industrial examples

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A B S T R A C T

At the end of process development or during a routine production period often rises the question to prove the identity or the significance of difference of processes or batches. To answer these questions objectively, relevant process data collected by computerised production equipment with recipe control and statistical tools are essential.

Attempts have been made to define some quantifiers to make process parameters comparable and to characterise processes. Three types of processes and equipments have been discussed and compared on the level of Accuracy, In-Process Precision and Repeatability of Input and Output parameters. The processes are:

1. Coating Process 1: Driam Vario 500/600 perforated drum coater and Fluid granulation Processes 1 and 2: Glatt WSG 15 top-spray granulator (version 1 with blow-off metal filter and version 2 with one chamber textile filter and mechanical shaking).

Computer programs have been developed to structure, organise and statistically evaluate process raw data collected by the above mentioned equipments. The results are presented in uniform summary tables for every batch following the recipe structure phase by phase.

The programs perform further statistical evaluation of summary tables, producing control charts.

These methods and tools are useful to filter out differences and unusual behaviour, to track back the original process, search the reasons and to understand the process.

The introduced Process Parameter Deep Analysis give the possibility to investigate filmcoating (or fluid granulation) process through the wetting curve (average moisture content vs. time).

The method helps process understanding and design of process optimisation.

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1. Introduction

In the 90s, when Validation concept was launched by Authorities in the Pharma Industry, in addition to product quality the importance of the Process came into the picture with more and more emphasis.

The age of Process Validation has started, and new computerised equipment appeared on the market.

Appearance and attempts of application of 21 CFR Part 11 slowed down the development/improvement because of its complexity and equipment regulation software non-compliance.

The Millennium born a new concept, new theories for GMP (the basic guiding rule for Pharma Industry), namely the Process Analytical Technology.

In this work a small part of this immense project is presented, i.e. what is possible with production equipment and processes, that are relatively new but definitely not designed for PAT, in order to collect information and prepare for real PAT environment.

1.1. Questions, problems

At the end of process development or during a routine production period when batches from the same process are produced often rise questions like:

- Were the bathes produced REALLY the same way?
- What is the difference between two runs of the same process?
- And for development purposes:
- When can be stated that two processes are significantly different?

To answer these questions we need relevant process data and statistical tools.

1.2. Equipment capabilities

A general Pharma Process can be almost exclusively characterised as a BATCH process. Hence, the product has a definite size in mass or volume, and the process has starting, middle and end phases for every batch.

Attempts to apply continuous processes [1,2], as a new tendency, appeared in the last few years only.
A consequence of the batch process application is that one of the main (financial) process optimisation targets is to reduce batch time, consequently, a batch process is frequently far from equilibrium, regarding especially the moisture balance.

At the end of the 90s pharmaceutical process equipments started to be equipped with modern sensors, regulated by PLC and PC control, and so become able to use so called “recipes”. A recipe is a structure of process steps (later called “phases”) defined in advance by the user software (see Section 2.3 for more details). Such softwares often have automatic data collection capabilities as well.

The collected (process) data are a goldmine of information about the process and equipment, but a typical user software is not prepared for further data processing.

1.3. Process analytical technology

In the scientific literature of pharmaceutical technology a new terminology and a new approach emerged around the Millennium. New scientific results, new (specially rapid) analytical methods, a lot of computerisation, and statistical evaluation methods become everyday development (and even production) tools for industry experts.


According to the Guidance [4] PAT tools for better process understanding are:

- Multivariate tools for design, data acquisition and analysis
  - Product and process design, with the tools of: statistical design of experiments (DOE), response surface methodologies, process simulation, pattern recognition.
- Process analysers
  - at-line, on-line, in-line.
- Process control tools

Design and optimisation of drug formulations and manufacturing processes:

- Identification and measurement of critical material and process attributes relating to product quality
- Design of a process measurement system to allow real time or near real time (e.g., on-, in-, or at-line) monitoring of all critical attributes
- Process control design to provide adjustments to ensure control of all critical attributes
- Development of mathematical relationships between product quality attributes and measured critical material and process attributes
- Continuous improvement and knowledge management:
  - data collection and analysis over product life cycle
  - knowledge base and scientific understanding of the relationships of: formulation-, process- and quality attributes
  - generalisation of problem solutions.

It is easy to recognise that different parts of the outlined structure are very coherent, i.e. improvement of one part initiates that of the others and vice versa.

Industry participants adopt these guides by their ability and capability, e.g. investment force, scholarship, production equipment quality (e.g., computerisation) level, analytical equipment abounding and variety, etc.

PAT initiates a cooperation between Academia and Industry as well, since the message of the guidance – by our reading – is that science based innovation must pervade the industry practice deeper and faster.

The Process Parameter Analysis, introduced in details below, is considered here as a tool for Process Analytical Technology, more accurately for Continuous Improvement. This approach is similar to that of Retrospective Process Validation was used as a special case of Process Validation. It gave lots of useful information about the process and product, and it was accepted by the authorities prior to (prospective) Process Validation procedures, but went out of practice later.

Although we hope that Process Parameter Analysis is more valuable and, since in its existing form it is a post-process tool, is going to be part of everyday practice, it is possible that after the introduction of on-line process analysers it will lose its importance.

2. Experimental

2.1. Data processing software

All equipments described below are highly computerised. Their computer systems regulate operation and collect process data as well.

Although i) a tremendous amount of data is generated during process development and routine production, ii) all equipments have data export capabilities, and iii) exported data are in a format that can be easily processed, no other tools are directly available for further data processing. The “report” files of exported data are sometimes simple data matrices containing the time in the first column and all the other data in the following ones.

The “report” files are sometimes structured to reflect the recipe structure and they occasionally contain some statistical data (average, minimum, maximum, and sometimes standard deviation), too.

Pharmaceutical equipments are quite unique in fine structure and configuration. There are no standards for control program content and format. The programs vary significantly from one equipment supplier to the other, and sometimes even from program version to the next, all originated from the same supplier.

What can be done with the collected data?

Directly almost nothing, more precisely it needs a huge amount of manual work (after importing the data file into, e.g. a spreadsheet program) to separate the data according to the recipe phases, analyse them and prepare statistics, and order the summary in a format useful for further processing since these data files are not as similar as it could be expected on recipe basis. The amount of data is threatening and the job to do is very inefficient: it needs high concentration but it’s boring and time-consuming.

It is quite evident that the solution is to develop some programs to work up the data files and extract the useful information. Let see how.

Process phases fall in two main categories with respect to set parameters, namely: steady-state (or practically steady-state) and non-steady-state phases.

Typically, pre- and post-Kernel phases (e.g. pre-heating, cooling) are non-steady-state. The time to reach new set points is comparable to the whole process time of the phase.

From the point of view of output parameters (typically Product and Outlet Air Temperature) a phase can be unsteady, even if all set parameters are constant. These output parameters are sensitive to the frequently unsteady moisture and heat balances. In case of fluid granulation, for example, an extended wetting during spraying causes considerable change in the product and outlet temperatures.

The inner structure of the process and the behaviour of the parameters can be analysed independently of each other (mostly for development purposes) or it can be looked for the correlation between the parameters in any phase.

A series of batches produced by the same process can be analysed for repeatability, to filter out the differences and to establish their reasons and consequences. This methodology provides a useful tool that supports failure analysis procedures and makes preventive action more effective.

The concept and results presented here are based on a research cooperation of Gedeon Richter Ltd. and Budapest University of
Technology founded [5] to mine out as much information as possible from the vast amount of data generated by development and routine production activities in a GR Pilot plant in recent years.

A data analysis software has been developed to process the data. The software is based on a systematic handling mechanism which is outlined in Section 2.5.

2.2. Equipments

Production and Pilot scale equipments have been equipped with modern automation and computerisation (with the highest level of control) for about a decade. In contrast, the software of these equipments has been continuously and radically developed ever since.

In this work two types of equipment have been compared. Although the unit operations they are used for are different, the most relevant parameters are identical, and targeted almost in the same range for both types.

Type-1 is a Glatt WSG 15 CD-A type top-spray fluid bed granulator (see flowchart in Fig. 1), type-2 is a Driam Vario 500/600 perforated drum film- and sugar coater system (see flowchart in Fig. 2).

There are two versions of the fluid bed granulator. Version 1 is a one chamber textile filter system with mechanical filter shaking, version 2 is a blow-off metal sieve dust filter system. Versions are referred to if distinction is significant.

The parameter list for both types of equipment is shown in Table 1. Process parameters can be divided into two main groups: i) input (or set) parameters and ii) output parameters without set points. Input parameters can be set independently to influence the status and behaviour of the material during the process. Output parameters reflect the effects of equipment and process on the product.

The separation of process and equipment parameters theoretically seem to be obvious, however, in practice it is quite difficult.

Since pharmaceutical processes are typically batch processes, any reduction in process time saves energy and improves capacity. That is the reason why short and highly non-steady processes are widespread.

2.3. Definition and structure of a typical process

In the literature, equipment information booklets, etc. where process descriptions can be found granulation and coating are described as processes where granulation or coating liquid (solution, dispersion or suspension) is sprayed onto a powder/tablet core causing the required effect, i.e. particle size enlargement or coating formation. In small equipment scale (table top or laboratory size) the processes are usually similar. The process definition contains the parameters of this Process Kernel (spraying) and sometimes an extra drying step. When newly developed processes are taken from lab to pilot or production scale, further pre- and post-Kernel steps (e.g. Equipment pre-heating, Charging, Pre-heating and Drying, Cooling, Discharging, see Fig. 3) have to be added in order to handle the material automatically during the whole production AND to balance the effect of batch to batch variations. The goal of the pre-heating steps is to start the granulation at the same (product or outlet air) temperature.

It is usual in a batch process that every first batch is a bit (or more) different from the rest since the equipment and the production room are still cold, filters are clean, etc.

If there are only 1 or 2 shifts in a plant (a usual practice at middle or pilot scale) or production runs are short, i.e. less than 10 batches (because of low market need or a frequent washing), the “first batch” effect cannot be neglected and has to be handled anyway.

In industrial practice the term “Process” means and has to mean all the steps (phases) including the pre- and post-Kernel steps, although they are assumed not to influence product quality significantly.

Fig. 1. Flowchart of Glatt WSG 15 CD-A type top-spray fluidization granulator.
The recipe handling user software of modern equipments contains these pre- and post-phases, but, obviously, the parameter sets are different from that of those for spraying and drying phases.

2.4. Concept of Process Parameter Analysis

For every equipment there is a chosen process, e.g. recipe that has been repeated for a higher number of times, useful for statistical Process Parameter Analysis.

<table>
<thead>
<tr>
<th>Type of parameter</th>
<th>Fluid bed granulator</th>
<th>Coater</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inlet Air Volume [m³/min]</td>
<td>Input + +</td>
<td></td>
</tr>
<tr>
<td>Inlet Air Temperature [°C]</td>
<td>Input + +</td>
<td></td>
</tr>
<tr>
<td>Inlet Air moisture content [g/kg dry air]</td>
<td>Input − +</td>
<td></td>
</tr>
<tr>
<td>Filter shaking time [s]</td>
<td>Input + n.a.</td>
<td></td>
</tr>
<tr>
<td>Filter shaking pause [s]</td>
<td>Input + n.a.</td>
<td></td>
</tr>
<tr>
<td>Spray Rate [g/min]</td>
<td>Input +</td>
<td></td>
</tr>
<tr>
<td>Atomizing air pressure [bar]</td>
<td>Input +</td>
<td></td>
</tr>
<tr>
<td>Fan air pressure [bar]</td>
<td>Input n.a.</td>
<td>If spec. spraying head available</td>
</tr>
<tr>
<td>Drum speed [rpm]</td>
<td>Input ±</td>
<td></td>
</tr>
<tr>
<td>Differential pressure [hPa]</td>
<td>Input n.a.</td>
<td>+</td>
</tr>
<tr>
<td>Product temperature [°C]</td>
<td>Output +</td>
<td>+</td>
</tr>
<tr>
<td>Outlet air temperature [°C]</td>
<td>Output +</td>
<td>+</td>
</tr>
<tr>
<td>Outlet air moisture content [g/kg dry air]</td>
<td>Output − +</td>
<td>+</td>
</tr>
<tr>
<td>Pressure drop on filter [Pa]</td>
<td>Output +</td>
<td>n.a.</td>
</tr>
<tr>
<td>Pressure drop on mesh [Pa]</td>
<td>Output n.a.</td>
<td>n.a.</td>
</tr>
</tbody>
</table>

n.a.: not applicable.

Table 1 Comparison of collected process parameters by Glatt WSG 15 CD-A type fluidization granulator and Driam Vario 500/600 film- and sugar coater system

Process Parameter Analysis has been carried out as follows. At first the individual processes have been evaluated. For the i-th batch several basic statistics have been calculated for every parameter in every phase, i.e. average, $\bar{x}_i$, standard deviation, $s_i$, minimum and...
maximum values, number of observations per phase, n, and a summary table has been produced.

From these summary tables an overall statistics has been computed for the whole series of k batches. An overall average and a batch-to-batch standard deviation have been calculated for every parameter and phase [6]:

\[
\bar{x} = \frac{1}{k} \sum_{i=1}^{k} x_i
\]

(1)

\[
s = \sqrt{\frac{1}{k-1} \sum_{i=1}^{k} (x_i - \bar{x})^2}
\]

(2)

Additionally, from the standard deviations an overall process standard deviation has been calculated:

\[
\bar{s} = \frac{1}{k} \sum_{i=1}^{k} s_i
\]

(3)

\[
s = \frac{\bar{s}}{c_4}
\]

(4)

where:

\[
c_5 = \sqrt{1 - c_4^2}
\]

(5)

\[
c_4 = \frac{\sqrt{2} \Gamma(\frac{3}{2})}{\sqrt{n - 1 - \Gamma(\frac{2}{2})}}
\]

(6)

and I() is the gamma-function.

Average and standard deviation control charts (so called x-charts and s-charts) have been produced from every parameter in every phase. Any batches significantly different from the rest can be recognised on this basis.

The control limits for x-charts and s-charts can be calculated as follows [6]:

\[
\mu = \bar{x} \pm z \frac{\bar{s}}{c_4 \sqrt{n}}
\]

(7)

\[
\sigma = \frac{c_5}{c_4} \bar{s}
\]

(8)

In addition to its use on control charts, it is very informative to check the difference between the target value and the calculated average value for every parameter in every phase.

2.5. Naming the child

In the Introduction part we were talking shortly about the Validation concept.

The pharmaceutical industry’s Validation concept (mentioned in Section 1) and the requirement system were developed (from the statistical point of view) for analytical method validation in great detail (note for example [7]). They are far less detailed for Process Validation on the level of process evaluation. The reason is quite evident: production equipments were (and still are) much less computerised than analytical equipments are, hence data collection and analysis is more complicated and less reliable.

Our equipments mentioned above have a good and reliable data collection system, hence data collection is not a problem. This situation can be generally expected in the whole industry in the future.

With the newly developed software data analysis is also possible, so we have all the tools to perform complex data analysis and evaluation.

According to the terminology developed for Analytical Method Validation, a system to evaluate a process can be defined as follows.

2.5.1. Accuracy of a Process Parameter

The accuracy of a process parameter expresses the closeness of agreement between the set value and the average of values found. It is calculated for every process parameter in every process step (phase).

\[
\text{Accuracy} = \frac{x_{set} - \bar{x}}{x_{set}} \times 100\%
\]

(9)

If the overall of averages (Eq. (1)) for a parameter of interest is the same as the set value, accuracy is infinite. As the offset is increasing, accuracy is decreasing.

Equipment structure and operation mode can influence accuracy. An example is discussed in detail in the results section concerning the fluid granulator with a mechanical filter shaking mechanism.

2.5.2. Intra-Process Precision of a process parameter

The Intra-Process (or In-Process) Precision of a process parameter expresses the closeness of agreement between the values found during a process step. It is calculated for every process parameter in every process step (phase).

The In-Process Precision of a process parameter can be well characterised by the average of standard deviations of the process parameter in the process step (phase) of repeated processes (Eq. (3)).

The In-Process Precision shows the ability of the process and equipment to keep a set value during a process step. This property is in close connection with the control system of the equipment. If the set value is the same in consecutive batches, or the controlled process can follow the change of a set value in short time compared to the phase length, In-Process Precision is good.

In-Process Precision of various parameters can be compared with each other, if the standard deviations are normalised with the overall parameter average, i.e. they are expressed as relative standard deviations. Priorities to decrease variances and to improve the process can be more clearly seen.

2.5.3. Repeatability of process parameters

For every process step (phase) the Repeatability of a process parameter expresses the precision between the averages of values found in repeated batches. It could be called as Inter-Process or batch-to-batch Precision as well.

The Repeatability can be well characterised by the standard deviation of averages (Eq. (2)).

For statistical reasons, in a properly running process, when small random deviations happen only, Repeatability (standard deviation of averages) is smaller then In-Process Precision (average of standard deviations).

On the other hand, it is a good signal for some irregular event, an possible operational, user or equipment fault, and the process has to be investigated, if Repeatability is greater then In-Process Precision.

3. Results

Three processes have been investigated and the Process Parameter Analysis results have been collected and they are shown in Tables 1–3 respectively. All the three tables consist of two parts, A and B. In Part A the set values, the overall of averages (Eq. (1)) and Accuracy (Eq. (9)) of every parameter in every phase are shown. In Part C the In-Process Precision and Repeatability can be seen for the same cases.

3.1. Accuracy of parameters

The Accuracy of Process Parameters has been compared for 3 processes concerning parameters with set values only. Accuracy of output parameters cannot be defined on output parameters having no set values.
3.1.1. Inlet Air Volume

Regarding Inlet Air Volume, Coating Process 1 (drum coater) has the best Accuracy. The second best is Fluid granulation Process 1 (fluid granulator with blow-off metal filter) and the worst is Fluid granulation Process 2 (fluid granulator with textile filter, mechanical shaking).

Considering the operation mechanism of the one chamber mechanical shaking system (e.g. during shaking airflow and spraying is switched off) the set value should be corrected as follows:

\[ x_{\text{corr}} = \frac{x_{\text{set}} \cdot \tau_{\text{pause}}}{\tau_{\text{shake}} + \tau_{\text{pause}}} \]  

(10)

Since \( \tau_{\text{pause}} = 110 \text{ s} \) and \( \tau_{\text{shake}} = 10 \text{ s} \), the set values have to be decreased by about 8%.

After the above correction the Accuracy of Fluid granulation Process 2 still remains the worst. A possible explanation is that after every switching back, the airflow control system needs time to recover and reach the set value.

3.2. Inlet Air Temperature

Pre-heating and Cooling phases are non-steady-state processes. As mentioned in Section 2.1, the set value of Inlet Air Temperature is far from that of the previous phase. The time it takes to reach the new set value is comparable to phase process time. Consequently, the Inlet Air, the Product and the Outlet Air Temperatures change during almost the whole process. For this reason, the above described simple statistical procedure is not adequate for these phases and the evaluation of Pre-heating and Cooling phases is not discussed in this work.

The process rankings with regard to the Accuracy of Inlet Air Temperature are similar to that of Inlet Air Volume. Coating Process 1 and Fluid granulation Process 1 are practically equal and the worst is Fluid granulation Process 2. Though Coating Process 1 is the only one

![Figure 4](image-url)
in which we can see changes in the set values between phases (Spraying 1–3 is set to 50, 55 and 60 °C, Drying to 50 °C), the Accuracy of Coating Process 1 is not worse than Fluid granulation Processes’. Other experiments not mentioned here have shown that fluid granulation processes are less accurate if set values change from phase to phase. Imperfect design of the heat exchanger (see details later) can be a possible explanation for this observation.

3.2.1. Spray Rate

In Pre-heating, Drying and Cooling phases there is no spraying, so Spray Rate is not applicable.

The best Accuracy of Spray Rate can be observed in Coating Process 1, the second in Fluid granulation Process 1 and the worse in Fluid granulation Process 2. The ranking remains the same even if the correction of set values (Eq. (10)) is applied.

Since the set values are not very close to each other, the comparison is not absolutely correct, but if it is considered that the control of a lower value is usually more difficult, the results will have a stronger emphasis.

It is interesting to note that the Accuracy of Spray Rate for Coating Process 1 in phase Spraying 4 is much worse than in other spraying phases. Checking the corresponding control x-chart (Fig. 5) shows that, although these batches were produced by the same recipe, they
3.3. In-Process Precision and Repeatability of Parameters

In-Process Precision (i.e. average of standard deviations) and Repeatability (standard deviation of the averages) show a much more complex picture than Accuracy of Parameters.

Usually In-Process Precision is worse than Repeatability, which is considered as a “normal” behaviour. If it happens to be the other way around, the reason has to be investigated. The outliers can be identified from the control s-chart, but it is necessary to go back to the problematic batch and phase. In order to find the reason, the diagram of parameters, the phase in question or the collected data themselves have to be checked.

3.3.1. Inlet Air Volume

The s-chart can reveal process problems even if the Accuracy (and x-chart) and In-Process Precision and Repeatability figures all look right. An example is shown in Figs 6–8 for Inlet Air Volume parameter in phase Spraying 1, Coating Process 1. Note that this process is the most stable one on the basis of Accuracy. Fig. 6 is an x-chart, where the y-axis has been magnified to make the confidence limits distinguishable. Apart from the s-chart, everything looks right: In-Process Precision and Repeatability figures in Table 2, x-chart is perfect, confidence limits are only 0.3% from the average. In-Process Precision is 8.1 m³/h (1.7% of average value), Repeatability is 0.5 m³/h (0.1% of average).

In contrast, in Fig. 7, the s-charts of the same parameter in the same phase, it can be seen that the standard deviation of batch no. 12 is an outlier.

In Fig. 8 the diagram of the batch and phase in question, where Inlet Air Volume is projected to the second y-axis, the value being 8 m³/min (all the other parameters are in sequence on the diagram as listed in the legend), it can be seen, that something unusual happened at about 10:58 (noted with an arrow). The effect appears in almost every parameter, but not as significant as for Inlet Air Volume. The LogSheet of the batch reveals an error message:

10:58 Disturbance DRUM DOOR OPEN.

It is now clear that the unusually high standard deviation of this parameter in this phase is due to the fact that the drum door was opened, and (for safety reasons) that stopped the machine for some seconds. Luckily, this problem did not have an influence on product quality. However, the above described procedure made it possible to track it down.

3.3.2. Inlet Air Temperature

Inlet Air Temperature is controlled the best in every equipment, In-Process Precision and Repeatability are good compared to the other parameters.

3.3.3. Spray Rate

The overall picture shown in Tables 2, 3 and 4 is that the most critical parameter is Spray Rate since Accuracy, In-Process Precision and Repeatability values are worse for this parameter in every type of process (or equipment) than for other parameters.

The reason of this phenomenon definitely goes back to a control problem. Although the dosing system is different in the processes, i.e. for the coater it is a peristaltic pump with frequency control by a balance, while for the fluid granulator it is a membrane pump with manual amplitude adjustment and frequency control by a mass flow meter, both control systems seem to be slower and less precise than that of those for other parameters.

An example is shown in Table 3 Part C. It can be seen, that In-Process Precision of Spray Rate is very bad in phases Spraying 1 and Spraying 3, but surprisingly good in phase Spraying 2.

A survey for possible reasons reveals the following facts: For this product the active ingredient is dissolved in the granulation liquid, so it is essential to spray all the granulation liquid to the granules from the first to the last drops (washing-in step included). When the flow meter becomes empty (or almost empty) it measures some extremely high but not real values because of bubble formation inside the meter. These unrealistic extreme values modify the averages and variances (specially the later) significantly.

The same reason could apply to the high standard deviation resulted in phase Spraying 3 (Fig. 9, last 4 parameters are projected to the second y-axis). as it is in Phase Spraying 1.

3.3.4. Output parameters

In contrast to input parameters output parameters show worse In-Process Precision than Repeatability that presume uncertainty and hidden effects of the product and the equipment. This phenomenon needs deeper and more detailed examinations.

3.4. Effect of a Pre-heating phase on process scale-up

In a fluid granulation process trip-points are defined in the recipe for every phase, i.e. when the phase has to be finished and the next phase has to be started. For a pre-heating trip-point (to start spraying) usually a product (or sometime an outlet air) temperature is specified.

Scaling-up the process, e.g. from pilot to production, it is a general rule to keep the inlet air temperature and the trip-point definitions the same.
The inlet air-, product- and outlet air temperature profiles of pilot and production scale processes can be seen on Figs. 10 and 11.

In both cases, the Pre-heating phase inlet air temperature is 70 °C, and the trip-point is set for product temperature at 30 °C.

However, there is an obvious difference between the pilot and the production scale process. When 30 °C product temperature is reached, inlet air temperature in pilot scale is about 52 °C, meanwhile in production scale it is about 74 °C. Consequently, when pilot scale

### Table 4

<table>
<thead>
<tr>
<th>Fluid granulation Process 2</th>
<th>n = 16</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glatt WSG 15, top spray granulator (one chamber textile filter with mechanical shaking)</td>
<td></td>
</tr>
</tbody>
</table>

#### Averages

<table>
<thead>
<tr>
<th>Set values</th>
<th>Inlet Air Volume [m³/h]</th>
<th>Accuracy</th>
<th>Inlet Air Temperature [°C]</th>
<th>Accuracy</th>
<th>Spray Rate [g/min]</th>
<th>Accuracy</th>
<th>Atomizing air [bar]</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spraying 1</td>
<td>500</td>
<td>-27.0</td>
<td>60</td>
<td>-3.1</td>
<td>270</td>
<td>-24.0</td>
<td>2.0</td>
<td>-6.5</td>
</tr>
<tr>
<td></td>
<td>365</td>
<td></td>
<td>58.2</td>
<td></td>
<td>205</td>
<td></td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td>Spraying 2</td>
<td>650</td>
<td>-27.9</td>
<td>60</td>
<td>0.5</td>
<td>390</td>
<td>-28.8</td>
<td>2.0</td>
<td>-0.3</td>
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<td></td>
<td>469</td>
<td></td>
<td>60.3</td>
<td></td>
<td>277</td>
<td></td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td>Spraying 3</td>
<td>750</td>
<td>-26.6</td>
<td>60</td>
<td>-0.5</td>
<td>500</td>
<td>-27.0</td>
<td>2.0</td>
<td>-0.6</td>
</tr>
<tr>
<td></td>
<td>551</td>
<td></td>
<td>59.7</td>
<td></td>
<td>365</td>
<td></td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td>Drying</td>
<td>750</td>
<td>-40.9</td>
<td>60</td>
<td>-2.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>444</td>
<td></td>
<td>58.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Variances

<table>
<thead>
<tr>
<th>In-process</th>
<th>Inlet Air Volume [m³/h]</th>
<th>Inlet Air Temperature [°C]</th>
<th>dp Mesh WSG, Pa</th>
<th>dp Filter WSG, Pa</th>
<th>Product Temperature [°C]</th>
<th>Outlet Air Temperature [°C]</th>
<th>Spray Rate [g/min]</th>
<th>Atomizing air [bar]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spraying 1</td>
<td>127</td>
<td>3.4</td>
<td>338</td>
<td>1229</td>
<td>2.7</td>
<td>1.8</td>
<td>107.6</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>2.4</td>
<td>920</td>
<td>920</td>
<td>1.5</td>
<td>1.2</td>
<td>37.8</td>
<td>0.1</td>
</tr>
<tr>
<td>Spraying 2</td>
<td>161</td>
<td>2.0</td>
<td>574</td>
<td>1318</td>
<td>0.4</td>
<td>0.3</td>
<td>122.4</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>0.7</td>
<td>1217</td>
<td>926</td>
<td>1.3</td>
<td>1.3</td>
<td>40.7</td>
<td>0.0</td>
</tr>
<tr>
<td>Spraying 3</td>
<td>204</td>
<td>1.8</td>
<td>718</td>
<td>1400</td>
<td>0.3</td>
<td>0.2</td>
<td>179.0</td>
<td>0.1</td>
</tr>
<tr>
<td></td>
<td>61</td>
<td>0.6</td>
<td>1367</td>
<td>919</td>
<td>1.4</td>
<td>1.2</td>
<td>50.4</td>
<td>0.0</td>
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<tr>
<td>Drying</td>
<td>220</td>
<td>3.6</td>
<td>657</td>
<td>1777</td>
<td>4.0</td>
<td>2.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>85</td>
<td>3.4</td>
<td>1041</td>
<td>683</td>
<td>1.7</td>
<td>1.3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Part A: Set values, overall of averages and Accuracy of Fluid granulation Process 2.
Part C: In-Process Precision and Repeatability of Fluid granulation Process 2 (input parameters with grey background).
spraying starts, inlet air temperature is relatively far from the set point. It is still in a steep increase, but because of the effect of spraying, product temperature levels off and it remains very close to 30 °C. In contrast, at the same point in production scale, inlet air temperature is already close to the set point, its increase is already slow, so product temperature increases up to 35 °C and later decreases slowly during the phase. There is a significant difference between the outlet air temperature profiles as well.

It seems reasonable to say that the reason of these differences is the significantly different slope of the inlet air curves shown in Table 5.

The different slopes are consequences of the fact that the heating capacity of the inlet air heat exchanger unit at start (relative to 1 m³ air) is about 3 times higher in the production equipment than that of the pilot scale one.

The undesirable effect can be compensated in pilot scale by preheating the empty equipment or in production scale by executed Preheating phase with lower inlet air temperature.


The essence of granulation and coating processes is the moisture content change as a function of time on the surface of powder particles and granules or on the surface of tablet core. The moisture content change influences the granule and film coating formation dramatically.

If the equipment is able to measure inlet and outlet air moisture contents (like the coater mentioned above), data collection problem is solved, and the possibility to make a moisture balance calculation from the collected data is given.

Moisture balance calculation gives a deeper and more detailed access to process structure and to events happening during the process on fine scale.

Process Parameter Deep Analysis (PPDA) has been applied and is detailed in this part of this paper. PPDA can be listed under the previously mentioned PAT tools, for example under Data Acquisition and Analysis/Process Design tools or Process Control/Critical Parameter Identification tools. The use of PPDA is essential during development and very useful during the post-marketing period.

PPDA is not the statistical analysis (control chart preparation, etc. — as mentioned in [3] and [4]) of “set” and “result” parameters of a process, but it is a more essential analysis of process data measured and (electronically) collected by the equipment. For example “average” moisture and heat balance calculations for a batch, or temperature and moisture content calculations for some critical points (e.g. on a tablet surface) during a coating process.

In this paper one coating process example is presented and analysed.

The following data have been measured and collected (sampling frequency 5 s) by a perforated drum coater type Driam DRC Vario 500/600 computerised system:

- $V_{in}$ [m³/min] volumetric flow of inlet air (referred as Inlet Air Volume)
- $t_{in}$ [°C] inlet air temperature
- $t_{in \text{dp}}$ [°C] dewpoint of inlet air
- $n_{\text{drum}}$ [rpm] drum speed
- $\Delta p$ [hPa] differential pressure in the drum

<table>
<thead>
<tr>
<th>Equipment</th>
<th>Inlet Air Temperature curve</th>
<th>Heating capacity</th>
<th>Inlet Air Temperature curve</th>
<th>Heating capacity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Part 1</td>
<td>[°C/s/m³ air]</td>
<td></td>
<td>[°C/s/m³ air]</td>
<td></td>
</tr>
<tr>
<td>Production</td>
<td>$T=24-52°C$</td>
<td>8.9</td>
<td>$T=53-73°C$</td>
<td>2.6</td>
</tr>
<tr>
<td>Pilot</td>
<td>$T=32-52°C$</td>
<td>3.0</td>
<td>$T=52-72°C$</td>
<td>2.5</td>
</tr>
</tbody>
</table>

Fig. 9. Process Chart of Fluid granulation Process 1, batch no. 7, Phase Pre-heating and Spraying 1 showing disturbance in Spray Rate.

Fig. 10. Fluid granulation Process 3, Inlet Air, Outlet Air and Product Temperature profiles of Phase Pre-heating and Spraying 1 in Pilot scale.

Fig. 11. Fluid granulation Process 3, Inlet Air, Outlet Air and Product Temperature profiles of Phase Pre-heating and Spraying 1 in Production scale.

Table 5 Comparison of production and pilot size fluid granulators heating capacity in Preheating phase
Inlet Air Volume [m³/min] 8 8 8 8 10 10

Set values Phase 1 Phase 2 Phase 3 Phase 4 Phase 6 Phase 12
Min. [g/s] = Atomizing air pressure [bar] 0 1.6 1.6 1.6 0 0
Spray Rate [g/min] 0 30 50 60 0 0
Avg. [g/s] = Max. [g/s] = 0.0789 0.1707 0.3229 0.3709
RSD [%] = 71.7 86.6 26.1 20.9
Standard deviation [g/s] = 0.0663 0.0602 0.0503 0.0535 0.0776 0.0648

Table 6
Wetting Rate and coefficient of determination (R²) in Coating Process 2, Phase 1–Phase 12

Coating Process 2
Driam DRC Vario 500/600 perforated drum coater

<table>
<thead>
<tr>
<th>Wetting Rate [g/s]</th>
<th>n = 45</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Phase 1</td>
</tr>
<tr>
<td></td>
<td>Pre-heating</td>
</tr>
<tr>
<td>Inlet Air Volume [m³/min]</td>
<td>8</td>
</tr>
<tr>
<td>Inlet Air Temperature [°C]</td>
<td>50</td>
</tr>
<tr>
<td>Drum speed [rpm]</td>
<td>3</td>
</tr>
<tr>
<td>Different pressure [hPa]</td>
<td>−2</td>
</tr>
<tr>
<td>Spray Rate [g/min]</td>
<td>0</td>
</tr>
<tr>
<td>Atomizing air pressure [bar]</td>
<td>0</td>
</tr>
<tr>
<td>Min. [g/s]</td>
<td>−0.2982</td>
</tr>
<tr>
<td>Avg. [g/s]</td>
<td>−0.0924</td>
</tr>
<tr>
<td>Max. [g/s]</td>
<td>0.0789</td>
</tr>
<tr>
<td>Standard deviation [g/s]</td>
<td>0.0663</td>
</tr>
<tr>
<td>RSD [%]</td>
<td>71.7</td>
</tr>
</tbody>
</table>

R²
Min. = 0.0475 0.0003 0.9352 0.9837 0.2190 0.0003
Avg. = 0.6767 0.9123 0.9940 0.9983 0.8976 0.7283
Min. = 0.9922 0.9994 1.0000 1.0000 0.9996 0.9998
No. of cases R² < 0.5 8 2 0 0 2 12

A fit of Eq. (14) to the latest modified data of International Association for the Properties of Water and Steam IAPWS [10] gives constants as (set 3):

\[ \begin{align*}
A_3 &= 619.465 \\
B_3 &= 7.258892 \times 10^{-2} \\
C_3 &= 2.934655 \times 10^{-4} \\
D_3 &= 9.744975 \times 10^{-7} \\
E_3 &= 1.876250 \times 10^{-9} 
\end{align*} \]

Eq. (14) has been used with constants set 3 for the calculation of saturation pressure.

The flow of moisture in the inlet/outlet air can be given [11] by Eq. (15):

\[ x = \rho_{\text{steam}} V \]

Inlet volumetric air flow is measured. The outlet volumetric air flow is:

\[ V_{\text{out}} = V_{\text{in}} \frac{P_{\text{dryair, out}}}{P_{\text{dryair, in}}} \]

\[ P_{\text{dryair, out}} = P - P_{\text{dp, out}} \]

The density of steam [11]:

\[ \rho_{\text{steam}} = \frac{M_{\text{steam}} P_{\text{dp, out}}}{RT} \]

where:

\( M_{\text{steam}} \) average molecular weight of water
\( P \) pressure of air (total)
\( P_{\text{dp, out}} \) saturation pressure of (inlet/outlet) air at dewpoint temperature
\( R \) universal gas constant.
The differential moisture balance (neglecting the atomizing/spray air) can be given as follows:

\[ x = \frac{dX}{dt} = \frac{dX}{dt} \]

\[ \frac{dX}{dt} = W(1 - c_{Ds}) + \rho_{\text{stream}} V_{\text{in}} - \rho_{\text{stream}} V_{\text{out}} \]

where:

\[ \Delta t = t_2 - t_1 = 60V_{\text{equipment}}/V_{\text{in}} \]

(assuming a plug flow of air in the equipment)

The integral moisture balance is:

\[ X = \sum_{k=1}^{n} \Delta X(t_k - t_{k-1}) \Delta t_k. \]  

4.1. Results and experiences of moisture balance calculation

4.1.1. Evaluation of a series of processes

Coating Process 2 has been evaluated as it is described in the first part of Section 2.5 with the addition of an extra step, the integral moisture balance calculation by Eq. (23).

The rate of wetting (or drying) can be characterized by the slope of the integral moisture balance curve. Some statistics of wetting rate (minimum, average, maximum, standard deviation, relative standard deviation) and the coefficient of determination, \( R^2 \) (minimum, maximum, number of cases, where \( R^2 < 0.5 \)) are presented in Table 6.

It can be seen, that:

- Wetting occurs in phases Spraying 1 and 2 and 3 (e.g. average wetting rate is positive), meanwhile drying takes place in phases Pre-heating, Drying and Cooling (average wetting rate is negative).
- Pre- and post-Kernel phases (Pre-heating and Cooling) are unsteady and uncertain regarding wetting rate as well. It is shown in the variations of wetting rate during these phases, which is much higher than in the Kernel Phases (Sprayings and Drying).
- Variation of wetting rate is relatively high (about 20%) even in the best case (Phase Spraying 3).
- Variation in wetting rate is in close correlation with the number of cases where coefficient of determination is small (say \( R^2 < 0.5 \)). These batches have to be investigated.
- Fitting a straight line on to the integral moisture balance usually gives a good result. Coefficient of determination averages above 0.99 in the best cases. Despite the fact that there are some (more or less) extremely low values, the average is about 0.7.

There is a common belief, that drying processes are sensitive to the change of seasons, e.g. according to the temperature and humidity of environmental air. The drum coater discussed in this paper is equipped with an Air Handling Unit, that is able to reduce the inlet air moisture content to a certain limit using a cooler (cooling media temperature 6–12 °C). Wetting of air is not possible.

Despite any expectations, a chart of wetting rate over 7 years of production (Fig. 12, x-axis being month of the year) shows no significant correlation with seasons.

A plot of wetting rate against the date of production (Fig. 13, x-axis is in months) to see the long term tendency shows no significant tendencies. No doubt, there is a slight decrease with time, starting roughly somewhere after year 2 or 3.

4.1.2. Evaluation of optimisation of a process

An optimisation procedure has been carried out for Coating Process 3 using 4 experiments.

Each trial consisted of 2 phases with different Inlet Air Temperature and Spray Rate (inlet air flow: 8 m³/min each).

![Fig. 12. Correlation of Wetting Rate with season periods in Coating Process 2, Phase 4 Spraying 3.](image)

![Fig. 13. Wetting Rate change in long term of Coating Process 2, Phase 2 and 3 and 4 Sprayings 1 and 2 and 3.](image)

<table>
<thead>
<tr>
<th>Trial no.</th>
<th>1/1</th>
<th>1/2</th>
<th>2/1</th>
<th>2/2</th>
<th>3/1</th>
<th>3/2</th>
<th>4/1</th>
<th>4/2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inlet Air Temperature [°C]</td>
<td>55</td>
<td>55</td>
<td>80</td>
<td>75</td>
<td>80</td>
<td>80</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>Spray Rate [g/min]</td>
<td>30</td>
<td>40</td>
<td>60</td>
<td>70</td>
<td>60</td>
<td>80</td>
<td>65</td>
<td>80</td>
</tr>
<tr>
<td>Wetting Rate [g/min]</td>
<td>2.6</td>
<td>6.3</td>
<td>8.3</td>
<td>10.0</td>
<td>8.4</td>
<td>12.1</td>
<td>11.1</td>
<td>13.1</td>
</tr>
<tr>
<td>Product Temperature [°C]</td>
<td>38.5±0.7</td>
<td>38.9±0.4</td>
<td>47.1±1.0</td>
<td>48.5±0.9</td>
<td>48.3±0.9</td>
<td>49.2±0.3</td>
<td>47.4±1.0</td>
<td>48.3±0.2</td>
</tr>
<tr>
<td>Outlet Air Temperature [°C]</td>
<td>36.8±1.4</td>
<td>38.7±0.2</td>
<td>43.1±1.4</td>
<td>46.4±0.4</td>
<td>43.6±1.4</td>
<td>46.4±1.1</td>
<td>42.5±1.1</td>
<td>45.1±0.3</td>
</tr>
<tr>
<td>Moisture excess [g]</td>
<td>284</td>
<td>276</td>
<td>276</td>
<td>276</td>
<td>250</td>
<td>250</td>
<td>250</td>
<td>250</td>
</tr>
<tr>
<td>Moisture excess [%(m/m)]</td>
<td>1.31</td>
<td>1.28</td>
<td>1.16</td>
<td>1.16</td>
<td>1.16</td>
<td>1.16</td>
<td>1.16</td>
<td>1.34</td>
</tr>
</tbody>
</table>
Table 7 shows the most important set and output parameters including Wetting Rate as a result of Process Parameter Deep Analysis.

A chart has been produced (Fig. 14) in search for a correlation between set and output parameters. Parameters to correlate were Spray Rate and Inlet Air Temperature vs. Wetting Rate, Product and Outlet Air Temperature. Marker shapes refer to Inlet Air Temperature levels: 55, 70 and 80 °C are noted with rhomboid, square and triangle markers respectively. Marker sizes are related to parameter type: Product Temperature, Outlet Air Temperature and Wetting Rate are denoted with big, medium and small markers respectively.

These above mentioned chart types seem to be useful for process and product design. They show how to set input parameters in order to get the required output parameter (e.g. product temperature).

4.2. Error propagation in moisture balance calculations

If the random error of the measured parameters are independent, the variance of moisture flow is a weighted sum of the component variances:

$$\text{Var}(X) = \sum_{i=1}^{m} \left( \frac{\partial x_i}{\partial y_j} \right)^2 \text{Var}(y_j).$$

(24)

There are eight measured parameters in the moisture balance, the partial derivatives being:

$$\frac{\partial x}{\partial w} = (1 - c_{\text{ds}}) \quad \frac{\partial x}{\partial v_{\text{in}}} = \rho_{\text{steam}} - \rho_{\text{steam}} \frac{\rho_{\text{in}}}{\rho_{\text{dryair}}}$$

(25)

$$\frac{\partial x}{\partial t_{\text{dp}}} = \rho_{\text{in}} \left( \frac{\rho_{\text{in}}}{\rho_{\text{dryair}}} + \frac{\rho_{\text{in}}}{\rho_{\text{dryair}}} \right) d_{\text{sat}}(t_{\text{dp}})$$

(26)

$$\frac{\partial x}{\partial t_{\text{in}}} = 1$$

(27)

where

$$d_{\text{sat}}(t_{\text{dp}}) = B + 2C t_{\text{dp}} + 3D t_{\text{dp}}^2 + 4E t_{\text{dp}}^3 \quad \frac{\partial x}{\partial t_{\text{out}}} = 0$$

(28)

$$\frac{\partial x}{\partial t_{\text{out}}} = \rho_{\text{out}} \frac{\rho_{\text{out}}}{\rho_{\text{dryair}}}$$

(29)

$$\frac{\partial x}{\partial t_{\text{in}}} = \frac{1}{T_{\text{in}}}$$

(30)

$$\frac{\partial x}{\partial t_{\text{out}}} = \frac{1}{T_{\text{out}}}$$

(31)

$$\frac{\partial x}{\partial t_{\text{in}}} = \frac{1}{T_{\text{in}}}$$

(32)

$$\frac{\partial x}{\partial t_{\text{out}}} = \frac{1}{T_{\text{out}}}$$

(33)

From initial calculations (numerical derivation of the parameter-time curves) it seems that four parameters, namely Inlet Air Volume ($v_{\text{in}}$), Dew point of Inlet Air ($t_{\text{dp}}$), Spray Rate ($w$) and Dew point of Outlet Air ($t_{\text{out}}$) out of the whole set of eight have almost equal but significantly higher influence on the error of the moisture balance, that the rest four.

5. Discussion

Computer programs have been developed to structure, organise and statistically evaluate (on basic level) process raw data collected by recipe controlled computerised equipment. The processed data are presented in uniform summary tables for every batch.

The evaluation procedure follows the recipe structure and separates the data phase by phase.

The programs have been designed to perform a further statistical evaluation of summary tables, to produce assorted data from the batch summaries and to make tendency analysis by control charts.

The tool developed is very useful to filter out differences and unusual behaviour by the use of average and standard deviation control charts (so called x- and s-charts) and to make it possible to design any other type of charts (e.g. to follow one or more parameters in a production series, to find correlation between parameters, etc.).

If an unusual behaviour is found, it is possible to track back the original process and search for the reason, to check parallel, neighbouring and similar processes to understand general behaviour and to prevent fault repetition if possible.

Calculated data produced by the programs are more useful for sophisticated statistical analysis (e.g. Principal Component Analysis) than the ones collected from batch records.

Process Parameter Analysis can reveal user equipment errors, maintenance or calibration problems, it can point out equipment handling differences. Corrective actions help develop manufacturing practice and improve quality.

Attempts have been made in this work to define some quantifiers, namely Accuracy, In-Process Precision and Repeatability to make process parameters comparable and to characterise processes.

Three processes have been discussed and compared on the level of Accuracy, In-Process Precision and Repeatability of Input and Output parameters. The processes are Coating Process 1: a Driam Vario 500/600 perforated drum coater and Fluid granulation Processes 1 and 2: Glatt WSG 15 top-spray granulator (version 1 with blow-off metal filter and version 2 with one chamber textile filter and mechanical shaking). Some differences between the processes have been found and identified. It is quite unlikely that the fluid granulator version 2 is accurate and precise enough (i.e. well controlled enough) for Process Analytical Technology requirements.

A Process Parameter Deep Analysis have been introduced to give the possibility to see a coating (and, potentially, fluid granulation) processes.
from a new aspect. The presented method makes it possible to investigate the film (or granules) properties as a function of wetting curve or moisture content vs. time. These are more relevant than product- or outlet temperatures, and give data about the final (residue) moisture content of the product, which can influence short and long term product properties, like hardness and stability, etc. The method helps process understanding and design of process optimisation.

References