Universidade de Lisboa
Faculdade de Farmácia

DESIGN AND IMPLEMENTATION OF AN ONGOING PROCESS VERIFICATION (OPV) PROGRAM

Bruna Hilário Estrela

Dissertation supervised by Professor Doctor João F. Pinto

Master Degree in Pharmaceutical Engineering

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Abstract

This thesis aimed to implement an Ongoing Process Verification (OPV) program, promoting the quality of the produced medicines, establishing a methodology on how to implement the program and to design a protocol based on a critical evaluation of the manufacturing process for a Medicine (solid oral form, tablet).

According to a defined Control Strategy, a Methodology was applied: Critical Quality Attributes (CQAs) and Critical Process Parameters (CPPs) were defined, and a process verification was carried out based on a detailed analysis of those parameters for Granulation, Drying and Compression process steps, for the chosen Medicine’s manufacturing process, using Statgraphics Centurion XVI software.

Throughout the analysis of the results, parameters with Out of Specification (OOS) results or low Process Capability Indices values were identified. Control charts and Process Capability Indices were used together for effective verification of the process state of control. In IPC parameters, Final Blend Loss on Drying (LOD) was identified as the most critical parameter because it was not in statistical control according to control charts and Process Capability Indices: $P_{pk\ (dosage\ 1)} = 0.33$; $P_{pk\ (dosage\ 2)} = 0.44$ ($P_{pk}<0.66$ is considered terrible). In Equipment parameters, for Granulation, Peristaltic Pump Speed was identified as the most critical parameter (not in statistical control) with $P_{pk\ (dosage\ 1)} = 0.20$ and $P_{pk\ (dosage\ 2)} = 0.27$. For Drying, Inlet Air Temperature, Inlet Air Volume, Outlet Air Temperature and Product Temperature parameters were not under control (all parameters presented a $P_{pk}<0.66$, for both dosages). For Compression, the Pre-Compression Force and the Output Rate parameters were not in statistical control ($P_{pk}<0.66$).

Overall, the factors influenced OOS results, the Equipment parameters were considered to have the highest influence in changes of the process that led to OOS values comparable to the IPC values – resetting specification ranges may be needed for that parameters. Although during the manufacturing process there have been OOS results and low Process Capability Indices, Drying and Compression parameters were the ones that presented a higher number of Equipment related parameters not statistically controlled, being the most critical process steps of the process.

Keywords: Control Strategy, Critical Process Parameters, Critical Quality Attributes, Ongoing Process Verification, Process Capability Indices.

Resumo

Esta tese visa implementar um programa de *Verificação Continuada de Processo*, promovendo a qualidade dos medicamentos produzidos, estabelecendo uma metodologia sobre como implementá-lo e conceber um protocolo baseado numa avaliação crítica do processo de fabrico de um medicamento escolhido (forma sólida oral, comprimido).

O medicamento considerado foi escolhido de acordo com a sua relevância para a empresa (por ser fabricado em grande número de lotes, ter duas dosagens e apresentar alguns problemas no processo de fabrico).

O fabrico de formas sólidas orais é efetuado de acordo com um processo rígido, com especificações muito rigorosas sobre parâmetros variáveis que são monitorizados de forma univariada e onde o controlo se baseia na verificação da qualidade pós-processo. Para compreender completamente o processo de produção de um comprimido, é necessário atingir alguns objetivos: explicar a variabilidade de lote para lote, prever-se de forma fiável se um lote será ou não bem-sucedido a partir dos dados em processo e analisar todos os fatores que afetam a qualidade.

A *Verificação Continuada de Processo* destina-se a garantir continuamente que o processo permanece controlado (o estado validado) durante o fabrico de um medicamento. A validação permite detetar desvios inesperados, bem como tendências dos resultados de cada parâmetro com impacto na qualidade final do produto promovendo a reavaliação do processo conduzindo à adoção de melhorias necessárias ao longo do ciclo de vida do produto. Existem vários benefícios provenientes da implementação da *Verificação Continuada de Processo*, destacando-se: a previsão do número de variações inesperadas no processo, que requerem investigação imediata e urgente; as melhorias do processo podem ser identificadas, justificadas e implementadas de forma mais eficiente; existem métodos mais robustos de controlo do processo e monitorização do processo de fabrico e os processos de revalidação podem ser evitados ou atenuados.

Um pré-requisito para a conceção de um plano de *Verificação Continuada de Processo*, é a existência de uma Estratégia de Controlo para o produto, gerando informação relacionada com o funcionamento do processo de fabrico. De acordo com a Estratégia de Controlo definida para a Gestão do Ciclo de Vida do Produto (Etapa 3A-fase de avaliação de um número definido de lotes - inclui a avaliação de parâmetros críticos de processo, atributos críticos de qualidade e estimativa da variabilidade e capacidade do processo e, a Etapa 3B - permite a deteção de falhas no processo e a monitorização da robustez do produto/processo

- realizada utilizando gráficos de controlo estatístico do processo e notificação de tendências), foi aplicada uma metodologia que permite a análise detalhada dos parâmetros de controlo em processo e parâmetros de equipamento, feita para as etapas do processo de Granulação, Secagem e Compressão necessárias ao fabrico do Medicamento escolhido.

Para identificar variações no processo de fabrico do produto, recorrer a ferramentas estatísticas é a única forma de descrever a "capacidade" de qualquer processo, ou seja, de avaliar os dados estatisticamente que podem resultar na prevenção de uma falha final se a causa da variabilidade puder ser descoberta e retificada antes de esta atingir uma magnitude significativa. Os Atributos Críticos de Qualidade (CQAs) e Parâmetros Críticos do Processo (CPPs) foram avaliados de acordo com ferramentas estatísticas de processo, tais como as cartas de controlo e os Índices de Capacidade de Processo (C_{pk} e P_{pk}), que constituem o cerne da análise da *Verificação Continuada de Processo*, recorrendo à utilização do software Statgraphics XVI (os dados são introduzidos no software sob a forma de um ficheiro Excel® e é possível tratá-los de acordo com as ferramentas estatísticas que se deseja utilizar). As cartas de controlo são a melhor ferramenta estatística para determinar se um processo está ou não em controlo estatístico, sendo utilizada para monitorizar os parâmetros críticos de processo e atributos críticos de qualidade com o objetivo de detetar a ocorrência de variabilidade. Quanto aos Índices de Capacidade de Processo, o C_{pk} compara a tolerância admissível com a propagação estimada do processo e mede o quão próximo o processo está do objetivo e quão consistente é com a sua capacidade média aproximada; o P_{pk} incorpora informação tanto sobre a dispersão do processo como sobre a média do mesmo, sendo assim uma medida como o processo está a decorrer, indicando quanta variação apresenta e como é que esta variação irá afetar a capacidade do processo de satisfazer os requisitos.

Através da análise de resultados, foram identificados parâmetros com resultados fora de especificação ou com baixos valores de Índices de Capacidade de Processo. As cartas de controlo e os Índices de Capacidade de Processo foram utilizados em conjunto para uma verificação eficaz do estado de controlo estatístico do processo. Nos parâmetros de controlo em processo (IPC), a Perda por Secagem na fase da Mistura Final foi o parâmetro identificado como mais crítico para o processo, uma vez que não estava em controlo estatístico de acordo com as cartas de controlo e os Índices de Capacidade de Processo $P_{pk\ (dosagem\ 1)} = 0.33$; $P_{pk\ (dosagem\ 2)} = 0.44$, $P_{pk}<0.66$ é considerado terrível. Quanto aos parâmetros de equipamento, para a Granulação, a Velocidade da Bomba Peristáltica foi identificada como o parâmetro mais crítico (não estava em controlo estatístico) para ambas as dosagens, através da observação das cartas de controlo e dos valores de Índices de Capacidade do Processo: $P_{pk\ (dosagem\ 1)} = 0.20$; $P_{pk\ (dosagem\ 2)} = 0.27$. Para a Secagem, a Temperatura do Ar de Entrada, o Volume de Ar de Entrada, a Temperatura do Ar de Saída e a Temperatura do Produto foram

os parâmetros que não estavam em controlo estatístico de acordo com as cartas de controlo e os valores de $P_{pk}<0.66$ em ambas as dosagens. Para a Compressão, a Força de Pré-Compressão e a *"Output Rate"* foram os parâmetros que não estavam em controlo estatístico para ambas as dosagens de acordo com as cartas de controlo e os valores de $P_{pk}<0.66$.

Em relação aos fatores que influenciaram os resultados fora de especificação, deve ser realçado que os parâmetros de equipamento tiveram mais influência nas mudanças no processo que levaram aos valores fora de especificação em comparação com os parâmetros de controlo em processo (IPC) – podem ser necessários rearranjos nos intervalos de especificação para esses parâmetros. Embora ao longo do processo de fabrico tenham havido resultados fora de especificação e baixos valores de Índices de Capacidade do Processo, os parâmetros de Secagem e Compressão foram os que tiveram mais parâmetros que não estavam em controlo estatístico, sendo assim consideradas as operações unitárias mais críticas no processo de fabrico.

O programa de *Verificação Continuada de Processo*, que pode ser implementado pela empresa, ajudará a identificar a causa e a reduzir a variabilidade identificada no processo.

Palavras-Chave: Atributos Críticos de Qualidade, Estratégia de Controlo, Índices de Capacidade de Processo, Parâmetros Críticos de Processo, Verificação Continuada de Processo.

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Table of Contents

List of Tables

List of Figures

List of Abbreviations and Symbols

A	Ampere	**N**	Newton
Alu	Aluminium	**NIR**	Near-infrared Spectroscopy
API	Active Pharmaceutical Ingredient	**OOS**	Out of Specification
CAPA	Corrective and Preventive Action	**OPV**	Ongoing Process Verification
C_{pk}	Process Capability Index	**PAT**	Process Analytical Technology
CPP	Critical Process Parameters	**PDCA**	Plan-Do-Check-Act
CPV	Continued Process Verification	**P_{pk}**	Process Performance Index
CQA	Critical Quality Attributes	**PQR**	Product Quality Review
CS	Control Strategy	**PQS**	Pharmaceutical Quality System
DMAIC	Define, Measure, Analyze, Improve and Control	**PVC**	Polyvinyl chloride
DoE	Design of Experiments	**PVDC**	Polyvinylidene dichloride
EMA	European Medicines Agency	**PVP**	Polyvinylpyrrolidone
FDA	Food and Drug Administration	**QbD**	Quality by Design
GMP	Good Manufacturing Practices	**RPM**	Revolutions per Minute
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use	**RTRT**	Real-Time Release Testing
IPC	In-Process Control	**SD**	Standard Deviation
LOD	Loss on Drying	**SOP**	Standard Operating Procedure
LSL	Lower Specification Limit	**SPC**	Statistical Process Control
mg/Tab	Milligram/tablet	**USL**	Upper Specification Limit
Min	Minute	**WHO**	World Health Organization
mm	Millimeter	**%**	Percentage

Glossary

Continued Process Verification (CPV)	Documented evidence that the process remains in a state of control during commercial manufacture.
Control charts	Successful Statistical Process Control tool used to determine whether a manufacturing of dosage form in pharmaceutical industry is in a state of statistical control or not. Can easily collect, organize and store information, calculate answers and present results in easy-to-understand graphs.
Control Strategy	A planned set of controls, derived from current product and process understanding that ensures Process Capability and product quality. The controls can include parameters and attributes related to active substance and finished product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control.
Critical Process Parameter (CPP)	A process parameter whose variability has an impact on a Critical Quality Attribute and therefore should be monitored or controlled to ensure the process produces the desired quality (ICH Q8).
Critical Quality Attribute (CQA)	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 (ICH Q8).
Define, Measure, Analyze, Improve, Control (DMAIC)	Intends to improve the Capability of a process by minimizing the variability over the most significant inputs of the process, with regard to the desired output, in order to optimize the performance of the process.
Holding Times	Can be considered as the established time period for which materials (dispensed raw materials, intermediates and bulk dosage form awaiting final packaging) may be held under specified conditions and will remain within the defined specifications.

Ongoing Process Verification (OPV)	Documented evidence that the process remains in a state of control during commercial manufacture.
Pareto Analysis	Quality Control tool that ranks the data classifications in the descending order from the highest frequency of occurrences to the lowest frequency of occurrences. The total frequency is equated to 100 per cent. The "*vital few*" items occupy a substantial amount (80 per cent) of the cumulative percentage of occurrences and the "*useful many*" occupy only the remaining 20 per cent of occurrences.
Plan-Do-Check-Act (PDCA) cycle	A *Plan-Do-Check-Act* methodology is a well-established way to structure joint efforts during innovation or continuous improvement.
Process Capability Index (C_{pk})	Potential of a process to meet a specification, used to determine the efficiency of the process.
Process Performance Index (P_{pk})	Incorporates information about both the process spread and the process mean and so is a measure of how the process is actually performing.
Process Validation	The documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce a medicinal product meeting its predetermined specifications and quality attributes.
Statistical Process Control (SPC)	Powerful collection of problem-solving tools to assess and improve process stability and Capability through the reduction of variability.

Note: Ongoing Process Verification (OPV) and Continued Process Verification (CPV) have the same meaning and their main difference is in the Regulatory Agency, CPV is used in the United States (by FDA) and OPV in Europe (by EMA). Throughout the thesis it will be used the term **Ongoing Process Verification (OPV) as it is the terminology used in Europe**.

1. Introduction

1.1 Background

Process Validation has been an activity well known throughout all industries, in particular the pharmaceutical industry. The first Food and Drug Administration (FDA) validation guidance, ***Guideline on General Principles of Process Validation***, goes back to 1987 [1]. **Process Validation** was defined as "*establishing documented evidence which provides a high degree of assurance that a specific process (such as the manufacture of pharmaceutical dosage forms) will consistently produce a product meeting its predetermined specifications and quality characteristics*" and concentrated predominantly on the importance of the three documented compliant validation batches [2].

However, through the years, only data from three batches was found to be not enough to warrant successful product manufacturing all over the product's lifecycle. In 2011, FDA issued the new ***Guidance for Industry – Process Validation: General Principles and Practices*** and introduced the concept of Lifecycle approach. Process Validation was no longer defined as an one-time event, but an ongoing activity from the design stage until the delisting of the product [2,3].

Both United States of America and European regulatory agencies and experts have been stating the same thing for a long time, which is: "*Companies should know, understand, and monitor their manufacturing process"*. European authorities and the International Council for Harmonisation (ICH) also have approached the question similarly: "*Know your process, be proactive, reduce variability, increase predictability, validate your tools, use statistically appropriate tools, and team collaboration is necessary"*. The monitoring guidelines are not prescriptive, which is good, because it permits companies to develop techniques that stick to their specific process and organization. Still, it can also result in confusion with regard to definitions and the specific tools, techniques, and resources needed. Additionally, there are a number of struggles that companies face when implementing Ongoing/Continued Process Verification programs [3,4].

According to FDA, **CPV is defined as "*Assuring that during routine production the process remains in a state of control*"**. FDA utilizes the ICH Q10 definition of "*state of control*" as "*a condition in which the set of controls consistently provides assurance of Continued Process Capability and product quality*." The FDA guidance outlines how CPV can be achieved for a particular production process through the collection and evaluation of Process Capability data by means of a officially documented CPV program [5].

In ***EU Guideline for Good Manufacturing Practice- Annex 15: Qualification and Validation*** [6], it is defined that:

- Manufacturers should monitor product quality to ensure that a state of control is maintained throughout the product lifecycle with the relevant process trends evaluated;
- The extent and frequency of OPV should be reviewed periodically. At any point throughout the product lifecycle, it may be appropriate to modify the requirements taking into account the current level of process understanding and process performance;
- OPV should be conducted under an approved protocol or equivalent document and a corresponding report should be prepared to document the results obtained. Statistical tools should be used, where appropriate, to support any conclusions with regard the variability and Capability of a given process and ensure a state of control;
- OPV should be used throughout the product lifecycle to support the validated status of the product as documented in the Product Quality Review. Incremental changes over time should also be considered and the need for any additional actions.

Modern Process Validation programs will require the adoption of the principles outlined in ICH Q8, Q9, and Q10 [7,8,9]. Good pharmaceutical development, as described in ICH Q8, is essential to the development of successful OPV implementation, not only through the identification of Critical Quality Attributes (CQAs) and their related Critical Process Parameters (CPPs), but also in the proper definition of the product and process Control Strategy (CS) on which to base the monitoring and control plan. Furthermore, the principles of ICH Q9, *Quality Risk Management* are important in the determination of sampling and monitoring frequencies and can play a very important role in the evaluation of process variation and prioritization of capability improvement actions [5].

Over the last 20 years there has been a significant development in presenting data to give confidence of safe, functional, and affordable medicines. The respective regulatory guidelines are good, but pharmaceutical manufacturers still often default to reporting if the process only meets specifications, with the statistical term being ignored [10].

A robust OPV program could provide the systems and capabilities associated with both the monitoring system for process capability, product quality and the management review system. These elements, once executed, will trigger the Corrective and Preventive Action (CAPA) system where required, which in turn should trigger the change management system.

Therefore, careful design and implementation of your OPV program will bring the elements necessary for transformation towards an ICH Q10 PQS-based [5].

To recognize variabilities in the product manufacturing process, statistics is the only way to describe a capability of any process in variability conditions. The data should be collected and statistically analyzed to look for trends [11].

1.2 Solid Oral Dosage Forms

Solid Oral Dosage Forms such as tablets and capsules are considered the most patient-acceptable dosage forms available today. Not only do they offer comfort and ease of handling, but also, they are extremely stable (chemical and physical), have a high throughput and are relatively low-cost to produce. Orally administered dosage forms are an intricate blend of pharmaceutical excipients and Active Pharmaceutical Ingredient (API) that must be suitably mixed and/or granulated to ensure the manufacture of acceptable pharmaceutical products [12, 13].

Typical pharmaceutical manufacturing processes contain a serious of unit operations, which includes machinery, methods, people, material, measuring systems and environmental conditions. To guarantee batch uniformity and integrity of medicine products, written procedures need to be established and followed to test for each batch. Such control procedures are settled to monitor the output and to validate the capability of the manufacturing process that may be responsible for causing variability in the characteristics of in-process material and the drug product [14].

The quality and performance of Solid Oral Dosage Forms depend on solid phase, formulation design, as well as on the manufacturing process. An important aspect of the relationship of dosage form processing to product quality is the prospects for process-induced solid phase changes of the API during manufacturing. Therefore, rational formulation and process designs need an integrated knowledge of polymorphism, interconversion mechanisms and available processing options. In order to insure consistent product quality, it is essential to predict, control or prevent phase transformation in process design and development [13].

1.3 Process Validation

1.3.1 Definition and Evolution

Process Validation is the documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce a medicinal product meeting its predetermined specifications and quality attributes [6].

Based on the guiding principles on Process Validation by European Medicines Agency (EMA), the approaches for Process Validations are as follows [15]:

1. Traditional Process Validation;
2. Continuous Process Verification;
3. Hybrid Approach;
4. Ongoing Process Verification (OPV) [15].

Note: Ongoing/Continu**ed** Process Verification **is not to be confused with the term** Continu**ous** Process Verification (Figure 1). "***Continued***" refers to ongoing, periodic (at predefined time points) review that provide "continual assurance that the process remains in a state of control (validated state) during commercial manufacture, while "***Continuous***" is an alternative approach to Traditional Process Validation wherein manufacturing Process Capability is continuously monitored and evaluated, as defined in ICH Q8 [7]. Continuous Process Verification is also described as an acceptable approach to Process Validation in EMA draft guideline on Process Validation [5,16,17].

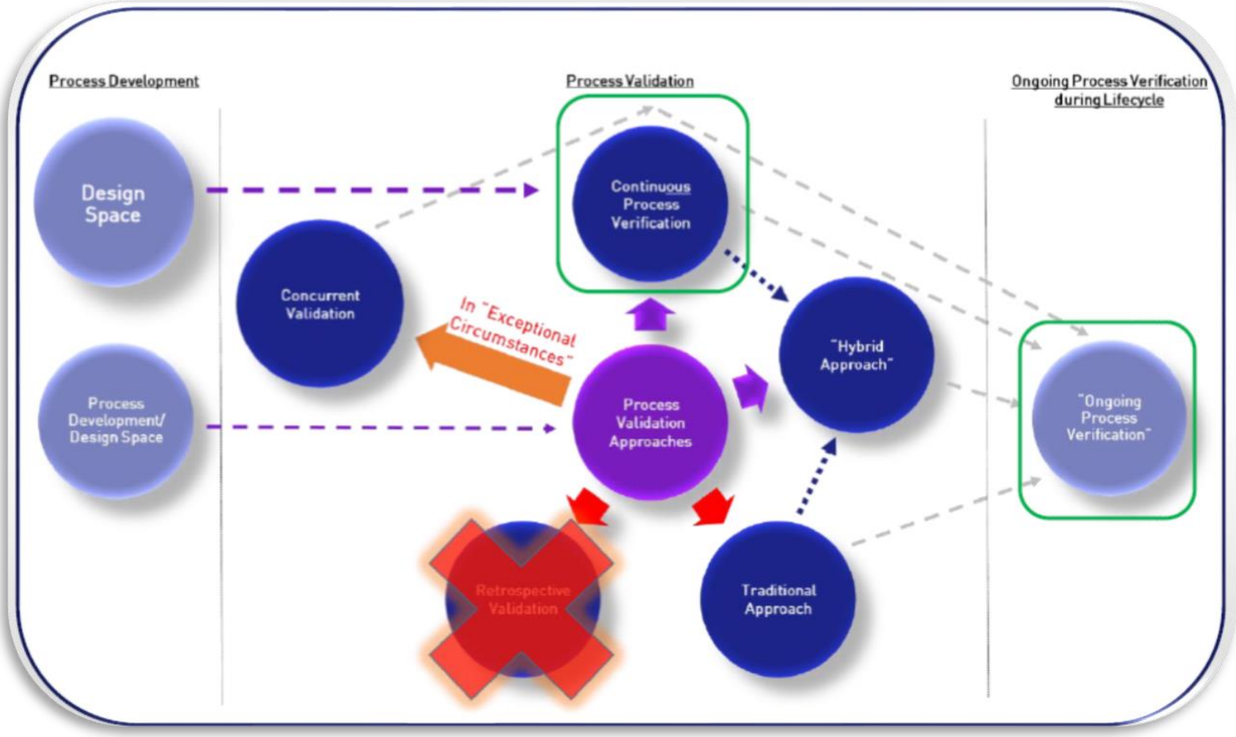


Figure 1- Continuous Process Verification and Ongoing/Continued Process Verification difference [16].

Process Validation data should be generated for all products to demonstrate the sufficiency of the manufacturing process. The validation should be carried out in accordance with Good Manufacturing Practices (GMP) and data should be held at the manufacturing location whenever possible and should be available for inspection. It is related with the collection and evaluation of data throughout the life cycle of a product – all phases in the life of a product from the initial development through marketing until the product's discontinuation – and provides scientific evidence that a process is capable of consistently achieving a quality product [18].

The evolution of Process Validation is represented in Figure 2, with the most important dates and events being recorded, highlighting the most important documents in Process Validation.

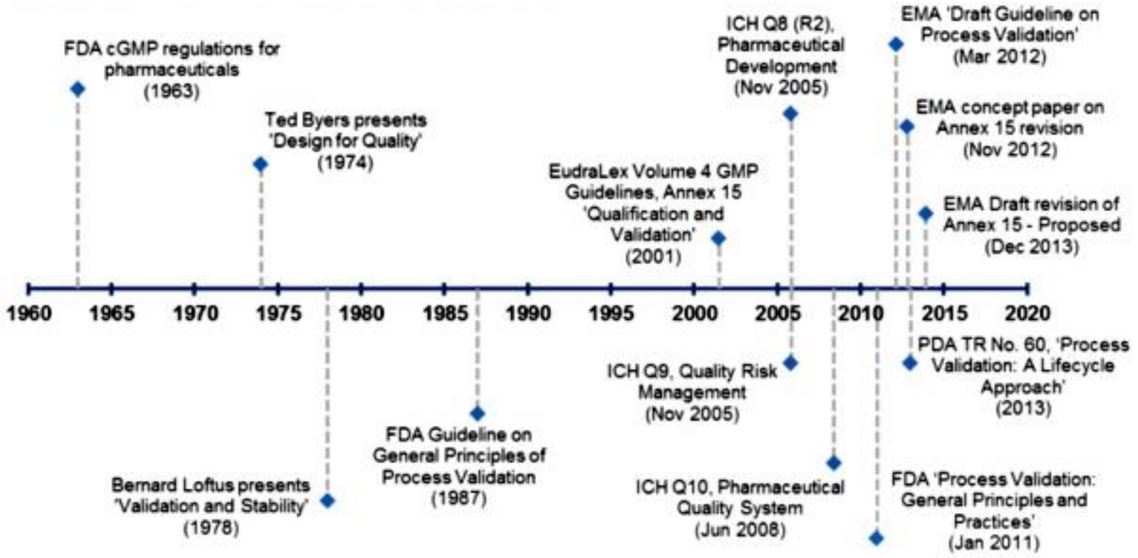


Figure 2- Evolution of Process Validation [5].

1.3.2 Objectives and Stages

The objectives of Process Validation must assure that [14]¹⁴[,18]:

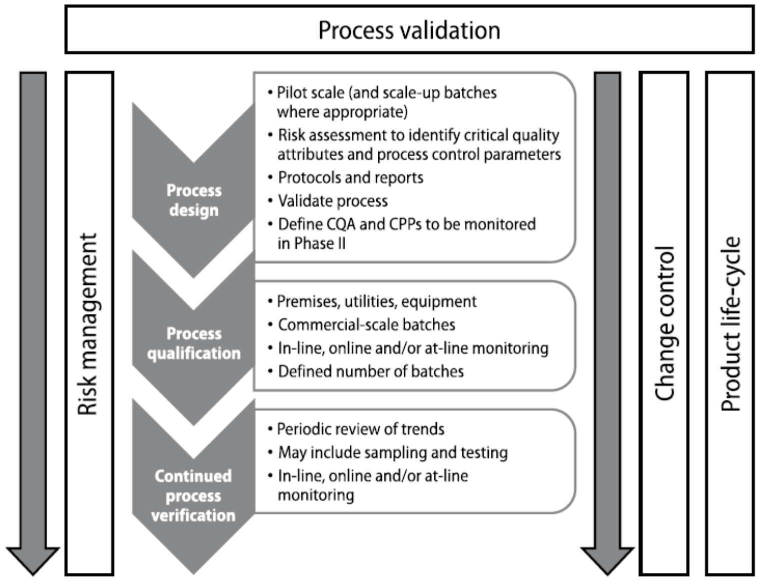
- The *process design* is evaluated to show that the process is reproducible, reliable and robust;
- The commercial manufacturing process is *defined, monitored and controlled*;
- *Assurance* is gained on a continuous basis to show that the process remains in a state of control;
- The existence of all necessary *quality assurance system* within organization;
- *Assurance of quality* of the product.

Process Validation is divided in three stages, shown in Figure 3, which are [18,19,20]:

- **Stage 1: Process Design** – The commercial process is determined based on scientific knowledge gained through development and scale-up activities;
- **Stage 2: Process Qualification –** The Process Design is evaluated and assessed to determine if the process is capable of reproducible commercial manufacturing;
- **Stage 3: Ongoing Process Verification** – Ongoing assurance is gained during routine production that the process remains in a state of control.

❖ Stage 3A and Stage 3B

These stages will be explained in Chapter 2 but, generally, OPV's **Stage 3A** is the initial phase where a defined number of batches undergo evaluation and the OPV's **Stage 3B** allows detection of potential process failures [21].



CQA, critical quality attribute; CPPs, critical process parameters.

Figure 3- Stages of Process Validation [18].

The critical steps and Critical Process Parameters (CPPs) should be identified, justified, documented and based on relevant studies carried out during the design stage and on process knowledge, according to the stages of the product life cycle [18].

CPP variability has an impact on a Critical Quality Attribute (CQA) and therefore should be monitored and/or controlled to ensure the process produces the desired quality. A CQA is "a *physical, chemical, biological, or microbiological property or characteristic of materials or* *products that should be within an appropriate limit, range or distribution to ensure the desired product quality"* [17,18].

1.4 Ongoing Process Verification (OPV)

1.4.1 Definition and Objectives

According to the Food and Drug Administration *(FDA)'s 2011 Guidance for Industry Process Validation: General Principles and Practices*, Stage 3 of the Process Validation Lifecycle, Ongoing Process Verification (OPV), is intended to provide "continual assurance that the process remains in a state of control (the validated state) during commercial manufacture". These activities must be part of a prospectively monitoring, including criteria for requisite actions "… *to correct, anticipate, and prevent problems so that the process remains in control*" [3,22,23].

OPV includes [3,22,23]:

- Preparation of a written plan for monitoring a pharmaceutical manufacturing process;
- Regular analysis of results;
- Documentation of the data collected;
- Analysis of data;
- Actions taken based on the results of monitoring the process.

The purpose of this Process Validation stage is to verify that the process is in a state of control and is performing consistently and in line with the process that was tested during the Process Qualification stage [5, 24].

The primary **objectives of OPV** are to [17,22]:

- Understand routine variability;
- Detect unusual variability;
- Identify specific opportunities and targets for process improvement.

OPV can be implemented at any stage of the process, i.e. [15]:

- To prepare Process Validation protocol during early commercial production;
- For continual improvement of the process through life cycle;
- For revalidation at commercial production.

This stage may be simply described as "maintaining validation" or "maintaining the validated state". It should be treated as extension to Stages 1 and 2 because all the scientific knowledge of operating space and its verification is done during Process Validation phases.

But this is still creating uncertainty because it is a new concept and the expectations stated in the 2011 Guidance are vague. The implementation of Stage 3 OPV reduces cost of quality, enhances product/process knowledge, and reduces regulatory compliance risks [19,25,26].

Through OPV, unplanned deviations as well as trends in input variables, in-process control (IPC) results, and final product quality are detected and an assessment made regarding necessary improvements throughout the life cycle of the product [24].

Data gathered during this stage might suggest ways to improve and/or optimize the process by altering some aspect of the process or product, such as the operating conditions (ranges and set-points), process controls, component, or in-process material characteristics. A description of the planned change, a well-justified rationale for the change, an implementation plan, and quality unit approval before implementing must be documented. Depending on how the proposed change might affect product quality, additional process design and process qualification activities could be warranted [3].

1.4.2 Benefits of OPV Implementation

The most important **benefits of OPV implementation** are [27]:

- It is anticipated the number of unexpected variations in the process can be reduced by in-depth knowledge of the process that generates information and knowledge to proactively and rapidly implement the necessary corrective actions;

- Process improvements can be identified, justified, and more efficiently implemented;

- Regulatory requirements for changes to or the granting of a marketing authorization in respect of changes to the manufacturing process may be reduced based on effective and continuous collection of process monitoring results;

- More robust methods for process control and manufacturing process monitoring existence;

- Revalidation processes can be avoided or alleviated.

A successful OPV program has systems in place which can proactively identify potential issues before they become critical [24]. As said before, an understanding of OPV can open on to consistent approaches, reduced investigation times and observations, the avoidance of lost batches and high-quality products [27].

1.4.3 Protocol

A good **OPV Protocol** should **minimally** include the following information [28]:

- **i.** Product information.
- **ii.** Personnel, roles, and responsibilities.
- **iii.** A structured table for all monitored parameters and variables corresponding to each attribute.
- **iv.** A description of the process for periodic examination of the limits and the method for adjusting limits based on updated process knowledge.
- **v.** Identification of the database warehouse and analysis software.
- **vi.** All relevant data and knowledge should be organized.
- **vii.** Description of planned analyses.
- **viii.** An appropriate action plan should be established to address deviating results. Procedures should be clearly defined regarding what kinds of aberrant results can be handled by designated personnel, and what results require escalation to upper management.
- **ix.** A plan for change management should be defined. Over the life cycle of the product, some aspects of the monitoring plan may need to be changed or updated due to an accumulation of experiences and process knowledge, or in response to regulatory requirements.

1.5 Statistical Process Control (SPC)

1.5.1 Definition

Statistical methods play an indispensable role in the quality improvement process in manufacturing and service industries [29]. **Statistical Process Control** is a powerful collection of problem-solving tools to evaluate and improve stability and Capability (defined later) through the reduction of variability [22]. It aims to monitor the method/procedure performance on an ongoing basis, detecting different types of unexpected results or if there are any significant changes in the process (trends or shifts) that require special attention [30].

Statistical Process Control techniques and data collection plans may also assist with the evaluation process as to the cause of variability. Statistical analysis of release and in-process data coupled with in-depth process knowledge achieved through risk assessment and criticality analysis supply the means of identifying opportunities to optimize the current process and/or identify areas where enhance detection mechanisms are required to ultimately improve end product quality [24].

There are two types of variability [30]:

- **Common cause**- that is a natural case of variability, management controllable and anticipated by mathematics rules. This is unavoidable but can be reduced. This variability has low risk and low cost, as it is predictable, controlled and in statistic control.
- **Special cause**- this is an un-natural case of variability, that is operator controllable and mathematics do not apply. This variation is preventable and can be eliminated, but it has high cost and high risk. This variability is not predictable and not controlled.

1.5.2 Tools

SPC tools, such as control charts and Capability/Performance analysis, form the analysis backbone of OPV [22].

A **control chart** (Figure 4) is the most successful SPC tool used to determine whether a manufacturing of dosage form in pharmaceutical industry is in a state of statistical control or not, it is used to monitor CQAs and CPPs to detect the occurrence of events of “special cause”. A control chart can easily collect, organize, and store information, calculate answers and present results in easy-to-understand graphs. It helps to record data and allows to recognize when an unusual event occurs. A computer collecting information in real time can even notice very slight changes in a process, and even warn you in time to prevent process errors before they occur [22].

Initially, control charts demonstrate how consistently process is performing, and whether one should, or should not, attempt to adjust it. Next, the statistical process control chart compares the Process Capability with standard pharmaceutical requirements, providing a Process Capability Index as an ongoing, accurate direction for quality improvement. Finally, control charts and its resulting Process Capability Indices quickly evaluate the results of quality initiatives design to improve process consistency [31].

The main purpose of using a control chart is to monitor, control and improve Process Capability over time by studying variation and its source. There are several functions of a control chart [31]:

- Provides statistical ease for detecting and monitoring process variation over time;
- Provides a tool for ongoing control of a process;
- Differentiates special from common causes of variation in order to be a guide for local or management action;

- Helps to improve a process to perform consistently and predictably to achieve higher quality, lower cost, and higher effective capacity;
- Serves as a common language for discussing Process Capability/Performance.

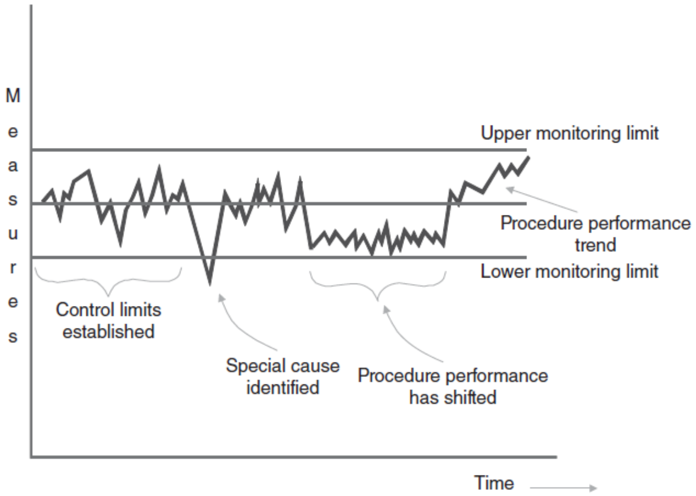


Figure 4- A control chart illustration [31].

Control charts do not relate the **Process Capability** to the customers' requirements because there is not any statistical or mathematical relationship between the standard specified limits and the process control limits. The *Process Analysis* is the bridge between the two; it compares the variability of an in-control and stable production process with its standard specified limit and **Process Capability/Performance Indices** are generated to demonstrate the reproducibility and consistency of a process [32,33].

The stability of the process refers to the ability of the process auditor to predict the process trends based on experience. A process is said to be stable if all the variables used to measure the Process' Capability have a consistent mean (within a specific range) and a consistent variance (within a specific range) over a sufficiently long period of time [32].

A capable process can produce products that consistently conform to specifications. Estimation of Process Capability measure how well the product meets the specifications. Capability is determined by comparing the process spread with the specification spread. Capability analysis evaluates how well a process meets a set of requirements defined by their specification limits. It is calculated by using a statistical data set for defining the system's Capability and engineering values. It includes three procedures [34,35]:

(a) An assessment of process control or stability;

(b) An assessment of the data for normal distribution and the requirement for data transformation;

(c) Estimation of the Process Capability/Performance Indices.

Process Capability Index, C_{pk} and Process Performance Index, P_{pk}, are often used to determine the efficiency of the process. The **C_{pk}** index compares the allowable tolerance of the process with the estimated process spread. It measures how close the process is to the target and how consistent the process is to approximately its Capability (Equation 1) [34].

Capability Index (C_{pk}) $= minimum \left\{\frac{sample\ mean - LSL}{3\ SD(within)}, \frac{USL - sample\ mean}{3\ SD(within)}\right\}$, (1)

where, USL and LSL are the upper and lower specification limits, respectively and $SD_{(within)}$ is the within-subgroup standard deviation, and sample mean is the average value of the individual observations [34,36].

P_{pk}, Process Performance Index, incorporates information about both the process spread and the process mean and so is a measure of how the process is performing and how much variation the process exhibits. The Equation 2 is used to calculate the overall Capability of the process [34]:

Performance Index (P_{pk}) $= minimum \left\{\frac{sample\ mean - LSL}{3\ SD(overall)}, \frac{USL - sample\ mean}{3\ SD(overall)}\right\}$,(2)

where, USL and LSL are the upper and lower specification limits, respectively and $SD_{(overall)}$ is the overall standard deviation that includes both within-subgroup and between-subgroup data [34,36].

C_{pk} and P_{pk} Rating and values according to Sigma level are represented in Table 3.

While C_{pk} references the variation to the specification limits, the P_{pk} index indicates how that variation will affect the ability of the process to meet the customer's requirements. Figure 5 represents a flowchart for the process improvement and Process Capability analysis procedure [34].

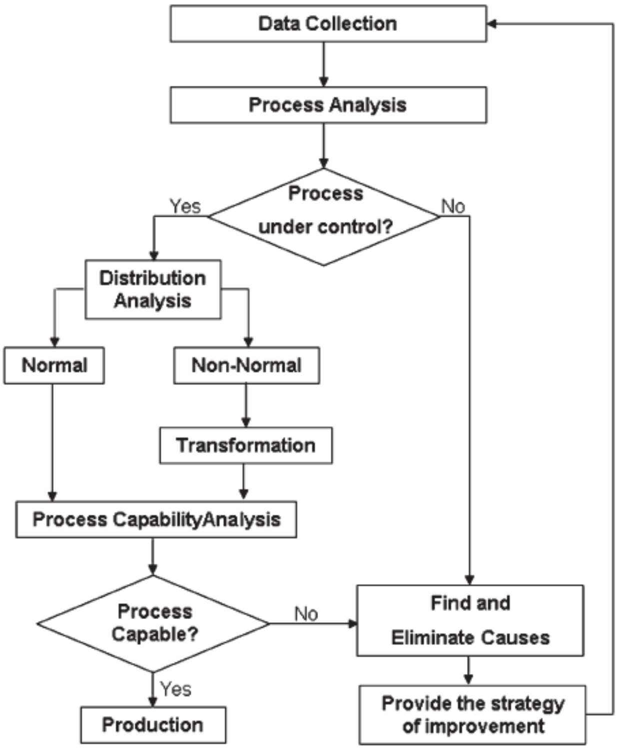


Figure 5- Flowchart for the process improvement and Process Capability analysis procedure [34].

2. Control Strategy (CS)

- **Control Strategy for Product Lifecycle Management – Stage 3A and Stage 3B**

A **Control Strategy** is a *planned set of controls, derived from current product and process understanding that ensures process capability and product quality*. The controls can include parameters and attributes related to active substance and finished product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control [37].

A pre-requisite to the design of an OPV Plan is the existence of a CS for the product, then provides information related to the operation of the manufacturing process. An appropriate set of CQAs) and CPPs are identified for monitoring as part of OPV (see Chapter 1) [27].

The **Stage 3A** is the initial phase of the Ongoing Process Verification stage. A defined number of batches go through Stage 3A evaluation. It includes assessment of Critical Process Parameters, Critical Quality Attributes, estimation of inherent process variability and Process Capability. Stage 3A analysis is a valuable resource for product development and future risk mitigation of similar products and processes. The discussed elements of Stage 3A inscribe the industry and regulatory guidance requirements, to provide enough data supporting risk-based decisions on the product. Fit for purpose statistical tools are applied during the assessment. In-depth Stage 3A enhances the product CS [21].

Routine monitoring process parameters and quality attributes are vital for detection of trends. The **Stage 3B** Ongoing Process Verification stage allows detection of potential process failures. The product/process robustness monitoring is typically performed using SPC charts and automated notification of trends are key aspects of Stage 3B. Stage 3B process warrants organizations to maintain an enhanced product CS and involved monitoring as well as decision-making based on a predetermined criterion. The assessment may result in tasks including continued close monitoring, enhancement of Control Strategy, or remediation project. Established statistical tools are employed as part of the ongoing assessment to guard against overreaction to individual events and avert failure to detect unintended process variability [21].

Modern methods of process control are [14]:

- Six Sigma;
- Process Capability/Performance Indices;

- Statistical Process Control (SPC) include sampling plan, experimental design, variation reduction, process capability analysis, process improvement plans.

Section 1.5 explains the way it is possible to monitor and optimize data according to Statistical Process Control, used tools and Process Capability/Performance Indices. Now, it is needed to define the Six Sigma Methodology, that is a disciplined, data-driven approach for eliminating defects in any process: from manufacturing to transactional and from product to service. The statistical representation of Six Sigma describes quantitatively how a process is performing [38].

In other types of industry, this methodology has already been implemented, since the quality standard implementation process is the best way to achieve the optimal results in quality progress and therefore in customer satisfaction. Once top management decides to implement this system in the Company, there are some obligatory changes that need to be done (i.e., process approach, customer focus, and continuous improvement) [38].

- **Six Sigma Methodology (DMAIC) applied on PDCA cycle**

The proposed framework for Six Sigma implementation has been developed with a reference to both the contextual elements (i.e., leadership) and the methodological techniques (i.e., PDCA). In terms of the contextual variables, it has been argued that the existence of a clear vision about Six Sigma projects is the key to the success of Six Sigma initiatives, where by relating these improvement projects to the business strategy management can enhance the effectiveness of Six Sigma projects [39].

Six Sigma is a structured methodology that attempts to achieve specific performance goals using statistical tools and techniques. Six Sigma is a systematic process where its success is contingent upon the existence and utilization of a disciplined approach towards process improvement. **Define, Measure, Analyze, Improve, Control (DMAIC)** (Figure 6) is widely used when a product or process is already in existence but performing inadequately. DMAIC focuses on eliminating unproductive steps, developing and applying new metrics, and using technology to drive improvement [39,40].

Figure 6- Six Sigma methodology (DMAIC) [39].

Since Six Sigma originated from the quality management field organizations can benefit from their Six Sigma initiatives if they frame it within the quality improvement paradigm. The **Plan-Do-Check-Act (PDCA) cycle** (Figure 7) is well established within quality management [40].

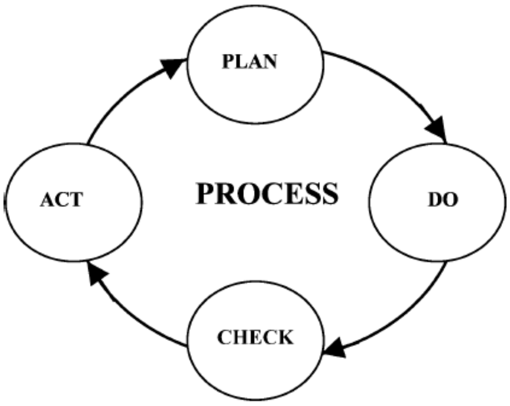


Figure 7- PDCA cycle [38].

Although incremental improvements to CS can emerge spontaneously throughout the life cycle of a product, improvements can be accelerated by a systematic approach to discovery and knowledge management. In modern quality management, many structured approaches have been defined and named; these tend to share certain important elements. One of the earliest and most influential is the **Plan-Do-Check-Act (PDCA)** methodology that is a model for learning and improvement that underlies Six Sigma provides an efficient manpower cultivation and utilization, by employing a "belt system" with clearly defined roles and responsibilities. Also, is a well-established way to structure joint efforts during innovation or continuous improvement and it is used to establish a Control Strategy for commercial manufacturing [41]. The four steps, conducted in repeated iterations and represented as the "PDCA wheel", can be described as follows [42]:

Plan: Identify needs and objectives and propose how to achieve the goal;

Do: Test the proposal for feasibility in a controlled environment;

Check: Study the result and draw conclusions;

Act: Define and implement the innovation or improvement.

To apply **Six Sigma methodology** use DMAIC, and, applying that to **PDCA cycle** will bring some advantages. Applying the **Six Sigma methodology** to the **PDCA cycle**, not only will improve the standard implementation, but also will improve the process. We apply the Six Sigma method to each part of the process, not only to the entire process (Figure 8) [38,39].

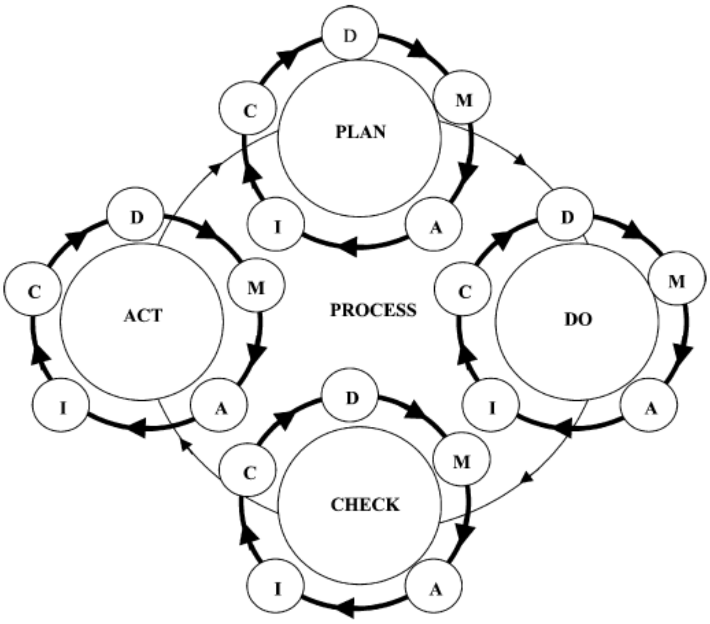


Figure 8- DMAIC applied on the PDCA cycle [38].

DMAIC for PLAN [38]

1. **Define** the objectives to improve the quality system.
2. **Measure** the Company Six Sigma level, gathering all the data.
3. **Analyze** all the data.
4. Establishing the **improvement** steps and tools conforming to the Six Sigma level.
5. Establish the **control** procedures. Develop control charts and plans.

DMAIC for DO [38]

1. **Define** priorities.
2. **Measure** each process distribution and Capability.
3. **Analyze** all the data for all the processes.
4. **Improvement** processes: implementing changes in order to correct the problems.
5. Check the **control charts** to verify the process improvement status.

DMAIC for CHECK [38]

1. **Define** clearly what were the objectives and what improvement processes have been implemented.
2. **Measure** the progress for each particular process.
3. **Analyze** the improvement process.

4. Establish if changes are to be done or **improvement** process will continue until now.
5. **Control** the checking process, all the data involved and how the measurements were done.

DMAIC for Act [38]

1. **Define** what are the next steps to continually improve the quality.
2. Take account of all quality indicators **(measure).**
3. **Analyze** the evolution of the Company quality system, measuring the customer's satisfaction and some other quality indicators.
4. Choose more powerful **improvement** tools, train new employees, try to impose higher quality standards to suppliers, implement new indicators, and so on.
5. Monitor all decisions that were made and **control** whether they respond to the quality improvement process.

While the PDCA cycle provides a framework for development and monitoring of new pharmaceutical processes, it can also be valuable in improving existing processes. Older products validated before the paradigm for ongoing validation was introduced can benefit in particular from this approach [42].

3. Thesis Organization

3.1 Thesis Outline

In **Chapter 1**, a **literature review** was made based on platforms from organizations such as International Council for Harmonization of technical requirements for pharmaceuticals for human use (ICHs), World Health Organization (WHO), Food and Drug Administration (FDA) and European Medicines Agency (EMA). The literature review was also based on articles regarding Ongoing/Continued Process Verification, Statistical and Engineering Tools. Generis® documentation – Standard Operating Procedures (SOPs) and Batch Master Record – concerning this matter were also used.

Chapter 2 presents the **Control Strategy** that was defined according to Stage 3A and Stage 3B combining with DMAIC methodology applied on PDCA cycle.

In **Chapter 3** was defined the **thesis outline**, **aim** of the thesis (what is expected with the project) and the **research hypothesis**.

In **Chapter 4**, the **Study Overview** was demonstrated with the **Methodology** for product lifecycle management (Stage 3A and Stage 3B application), **Methods**, **Instruments and Materials**.

In **Chapter 5**, a detailed **analysis of IPC** and **Equipment parameters** (for Granulation, Drying and Compression process steps) data was intended to understand batch-to-batch variation and variation of the parameters under study, in order to better control and monitor the manufacturing process of the Medicine. Furthermore, complaints for the Medicine in question were reviewed to understand the main reason for the yellowish color the tablet presented sometimes when sold to the public and the need to solve it. To analyze and identify the defects in the process, it was also important to understand at which stage of the process the most significant process losses occur that contributed to a decrease in yield (below specification).

In **Chapter 6,** an OPV Protocol was done for the Company with obtained results.

Chapter 7 has described the **final considerations** of the project, including **conclusions** and possible **future work**.

3.2 Aim of the Thesis

This work intended to contribute to the design and implementation of an Ongoing Process Verification program of a manufacturing process, establishing a methodology on how to implement it, and to design a protocol based on a critical evaluation of the manufacturing process for a Medicine (solid oral form, tablet).

OPV might be implemented as a system, completed with a strategy and plan for implementation and sustainability throughout the lifecycle of the process/product [43].

3.2.1 Hypothesis

The implementation of an OPV program in a manufacturing process

promotes the quality of the medicines manufactured.

4. Study Overview

4.1 Chosen Medicine

The Medicine chosen as a model to the construction of the Master's thesis was based on its high relevance for Generis® Farmacêutica, S.A., as it is manufactured in high number of batches, in the versatility of two dosages to explore and also due to some problems in process manufacturing reflected by the recurrent complaints that the Medicine presented.

4.2 Methodology

4.2.1 Stage 3A

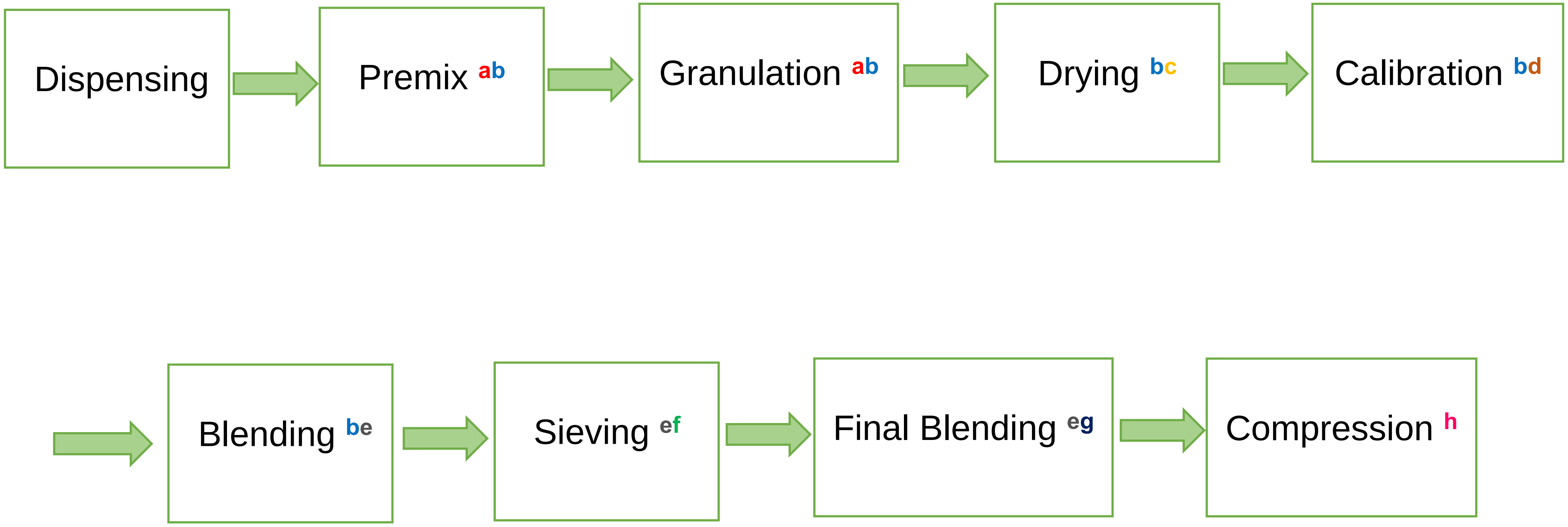
Stage 3A includes the evaluation of Critical Process Parameters, Critical Quality Attributes and Process Capability/Performance (see Chapter 2). Appropriate statistical tools were applied during the assessment and this step deepens the Medicine Control Strategy.

Stage 3A applied to the practical case:

1. From the Batch Master Records provided by the Company (from 2016 to 2020), several data sets, IPC parameters and Equipment parameters (described below) were taken into consideration.
2. A comparison of the parameters taken from the Batch Master Records with the parameters normally analyzed in the literature were established (Table 1).
3. For a better analysis of the process, a process flowchart (for dosages 1 and 2) was done based on Generis® Batch Master Record (Figure 9).
4. Critical Quality Attributes and Critical Process Parameters were defined to be analyzed later (Table 2).

Table 1- Comparison between the parameters analyzed in Generis® Farmacêutica, S.A. and the ones found in literature [14] with the identification of CQAs and CPPs to be monitored during manufacturing process.

Generis® Farmacêutica S.A. / Literature	**Mixture / Granulation**		**Drying**		**Final Blending**		**Compression**	
	IPC parameters (CQAs)	**Equipment parameters (CPPs)**	**IPC parameters (CQAs)**	**Equipment parameters (CPPs)**	**IPC parameters (CQAs)**	**Equipment parameters (CPPs)**	**IPC parameters (CQAs)**	**Equipment parameters (CPPs)**
Similarities	- Blend Appearance - Granulate Appearance - Loss on Drying	- Granulation end-point - Mixing Time - Mixer Speed - Solution Addition Time	- Loss on Drying	- Inlet Air Temperature - Inlet Air Volume - Outlet Air Temperature - Drying Time - Product Temperature - Dehumidify	- Loss on Drying	- Mixing Time - Mixer Speed	- Appearance - Diameter - Disintegration Time - Average Mass - Hardness - Friability - Thickness	- Pre-Compression Force - Compression Force - Fill Depth - Output Rate - Feed Shoe Settings
Differences Present in Literature but not in place in Generis® Farmacêutica S.A.	None	None	None	None	- Blend homogeneity (in Generis®, only performed for Process Validation batches)	None	None	None



Legend:

[a] Equipment A

[b] Equipment B

[c] Equipment C

[d] Equipment D

[e] Equipment E

[f] Equipment F

[g] Equipment G

[h] Equipment H

Figure 9- Medicine Process Flowchart.

Note: According to necessary quantity to produce the Medicine, the equipment was chosen to correspond the quantities needed.

Table 2- Defining the critical parameters to be analyzed.

IPC parameters (CQAs)	**Equipment parameters (CPPs)**			
	Granulation	**Drying**	**Final Blending**	**Compression**
- Average Mass - Diameter - Disintegration Time - Friability - Hardness - Loss on Drying Final Blend - Loss on Drying Granulate - Thickness	- Mixing Time - Mixer Speed - Granulator Speed - Solution Addition Time - Peristaltic Pump Speed - Granulation end-point	- Inlet Air Temperature - Inlet Air Volume - Outlet Air Temperature - Drying Time - Product Temperature - Dehumidify	- Mixing Time - Mixer Speed	- Pre-Compression Force - Compression Force - Fill Depth - Output Rate - Feed Shoe Settings

According to the parameters analyzed in the Literature and the parameters analyzed in the Company and also through the analysis of Batch Master Records, it was possible to define the critical parameters for analysis.

4.2.2 Stage 3B

Stage 3B was used to establish statistical tools employed as part of the ongoing assessment to guard against overreaction to individual events and prevent failure to detect unintended process variability [21] (see Chapter 2 – Control Strategy).

For process verification, a detailed analysis of IPC and Equipment parameters for Granulation, Drying and Compression (the critical process steps) data was done. To analyze data, **Excel®** and **Statgraphics® Centurion XVI software** was used, and were applied Engineering tools such as **Pareto analysis** (Quality Control tool that ranks the data classifications in the descending order from the highest frequency of occurrences to the lowest frequency of occurrences. The total frequency is equated to 100 per cent. The "vital few" items occupy a substantial amount (80 per cent) of cumulative percentage of occurrences and the "useful many" occupy only the remaining 20 per cent of occurrences [44]. Using Pareto analysis it is possible to analyze the defects and found major and minor contributors to those defects [45]), and Statistical Tools such as **control charts** and **Process Capability/Performance Indices**.

4.2.3 Six sigma methodology (DMAIC) applied to PDCA cycle

Throughout the collection of data and analysis process, the **DMAIC** methodology applied to the **PDCA cycle** was implemented (see Chapter 2).

DMAIC for Plan: The need for implementation of the OPV has been identified, as well as the objectives for implementing it. For implementing the OPV It is necessary to perceive routine variability, detect unusual variability and identify specific opportunities and targets to improve the process. Data were collected (Stage 3A, see section 4.2.1), the necessary statistical steps and tools (Stage 3B, see section 4.2.2) were established to improve the process, and the control charts were developed.

DMAIC for Do: Stage 3A and Stage 3B (see sections 4.2.1 and 4.2.2) implementation. The critical parameters of the process were identified (Table 2) and all graphs were plotted for analysis and discussion of results.

DMAIC for Check: Measure the progress of the process, control the checking process and all data involved.

DMAIC for Act: OPV program implementation. "Plan", "Do" and "Check" stages were done and then it is up to the Company, if agrees and decides to proceed with the OPV implementation, to put into practice the tasks corresponding to "Act" stage.

4.3 Methods

It is important to understand that in:

Pareto analysis, the batch indicated in the following Tables 4,5,6 and 7 is the one which represents more percentage of the total (100%) and it means that batch is the one with the Parameter value closest to the specification limits [45]. The Pareto chart helps to understand which batch had the most variation of data in a given parameter (i.e. Out of Specification) to understand if it is a unique case or if it might happen in other parameters of the same batch. If it happens, it is possible to conclude that something wrong happened in that particular batch.

Control chart, there are four possible results:

- All batches within specifications;
- Some batches below the Lower Specification Limit (LSL);
- Some batches above the Upper Specification Limit (USL);
- Some batches above and below the Specification Limits.

Process Capability/Performance Indices Analysis –Process Capability Index (C_{pk}) and Process Performance Index (P_{pk}) rating were considered (Table 3) [30,46].

Table 3- C_{pk} and P_{pk} Rating and values according to Sigma level [46].

C_{pk} and P_{pk}	Sigma Level	Capability/Performance Rating
0.33	1	Terrible
0.67	2	Poor
1.00	3	Marginally Capable
1.33	4	Capable
1.67	5	Good
2.00	6	Excellent

When it is possible to see the values proximity of the C_{pk} and P_{pk}, it shows the adjacency of the deviation of data, which shows the uniformity of variation, over time [47].

P_{pk} is a suitable alternative as it can determine an equivalent index to the C_{pk} when in statistical control and the P_{pk} is more sensitive to a process that is not in statistical control [10].

4.3.1 Product IPC Parameters Analysis - CQAs

The IPC parameters analyzed in Generis® Farmacêutica, S.A. were, as defined in Table 2:

- Granulate Loss on Drying (LOD);
- Final Blend LOD;
- Average Mass;
- Disintegration Time;
- Diameter;
- Friability;
- Hardness;
- Thickness.

4.3.2 Product Equipment Parameters Analysis – CPPs

4.3.2.1 Granulation Process Step

Granulation is the process of collecting particles by creating bonds between them. It is the most critical step in tablet manufacturing as virtually all tablet characteristics such as average mass, hardness, disintegration etc. depend on the granulation parameters [48].

For Granulation Process step, the Equipment parameters subject to control in Generis® Farmacêutica, S.A. were, as defined in Table 2:

- Mixing Time;
- Mixer Speed;
- Granulator Speed;
- Solution Addition Time;
- Peristaltic Pump Speed;
- Granulation end-point.

At this stage of the process, the batches were divided according to the equipment used for the Granulation process step. That is, there are batches where the Granulation was made in **Equipment A** and others in **Equipment B**, depending on the batch size. **Note**: Both dosages were produced in both equipment, according to the corresponding batch size.

To generate the graphs, it was not possible to evaluate the most parameters of the Equipment B since there the equipment works within a range of values and not with discrete values in each parameter (Annex I-Intermediate Graph Decision Tables). The parameters considered (due to the existence of discrete data and information) were for both dosages (**Granulation end-point**, **Peristaltic Pump Speed** in **Equipment A** and **Granulation end-point** in **Equipment B**).

4.3.2.2 Drying Process Step

This step involves drying of wet granules [48]. For Drying process step, the Equipment parameters subject to control in Generis® Farmacêutica, S.A. were, as defined in Table 2:

- Inlet Air Temperature;
- Outlet Air Temperature;
- Product Temperature;
- Inlet Air Volume;
- Dehumidify;
- Drying Time.

At this stage of the process, the batches were divided according to the used equipment for the Drying process step. Taking into account to the batch size, there are batches where the **Drying** was made in a **Equipment B** and others in **Equipment C**.

To generate the graphs, the parameters that could not be considered were Inlet Air Volume (dosage 2) because there was not a variation of values since they were all the same and could not be evaluated in the software (Annex I-Intermediate Graph Decision Tables) and Dehumidify and Drying Time parameters are only evaluated in Equipment B and there was not also a variation of values. Evaluated parameters were for **dosage 1** (**Inlet Air Temperature, Outlet Air Temperature, Product Temperature and Inlet Air Volume, all for Equipment C**) and for **dosage 2** (**Inlet Air Temperature, Outlet Air Temperature and Product Temperature, all for Equipment C**).

4.3.2.3 Final Blending Process Step

In Final Blending, the Equipment parameters subject to control in Generis® Farmacêutica, S.A. were, as defined in Table 2:

- Mixing Time;
- Mixer Speed.

To generate the graphs, the **parameters could not be considered** because there was not a variation of values, they were all the same and could not be evaluated in the software (Annex I-Intermediate Graph Decision Tables).

4.3.2.4 Compression Process Step

For Compression process step, the used equipment was two rotary tableting machines. The Equipment parameters subject to control in Generis® Farmacêutica, S.A. were, as defined in Table 2:

- Pre-Compression Force;
- Compression Force;
- Fill Depth;
- Output Rate;
- Feed Shoe Settings.

4.4 Instruments and Materials

The material used for the results analysis were Batch Master Record, the company's Complaints records, and Product Quality Review, as well as Statgraphics® Centurion XVI software.

4.4.1 Statgraphics® Centurion XVI

Statgraphics® (StatPoint Technologies, Inc.) is a general-purpose statistical package, its appealing use of graphics, together with its easy-to-use menu system, make it ideal as a tool to simulate and interest the user [32]. Statgraphics® Centurion XVI was provided by the company and was chosen to generate graphics for the statistical data analysis of the parameters. This software has statistical tools useful for data analysis, such as Pareto charts, control charts and Process Capability/Performance Indices. The data is entered into the software in the form of an Excel® file and it is possible to handle the entered data according to the tools wished to use [49]. The software overview is represented in Figure 10.

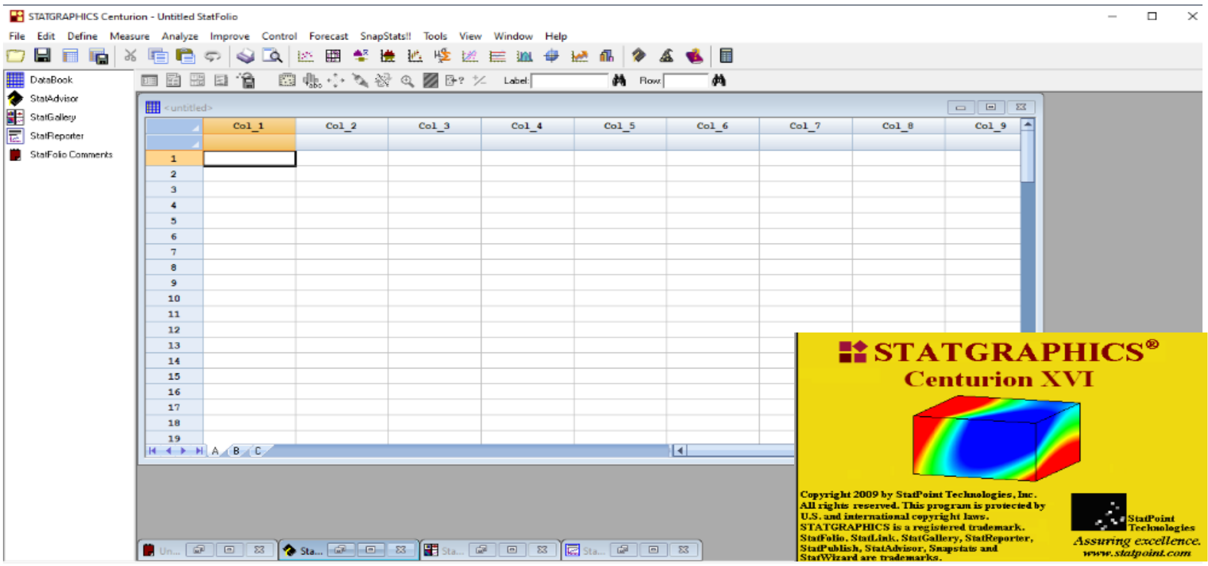


Figure 10- Statgraphics® Centurion XVI software overview.

5 Results and Discussion

Nowadays, Solid Oral Dosage Forms are manufactured in a safe, accepted and validated environment—manufacturing is carried out as a fixed, rigid process with very strict specifications on variables that are monitored in a univariate manner and where control is based on post-process quality checking. The problem with the current methods is their lack thorough process understanding of the manufacturing. The destructive and laborious finished product analysis—carried out only for a very little number of tablets—provides almost no information about the process itself. It thus adds nothing to process understanding, and this eliminates the chances of early fault diagnostics. To fully understand tableting or any other process, a goal is achieved when one can explain batch-to-batch variability, can reliably predict if a batch will be successful or not from the in-process data, and all factors affecting quality have been observed [50].

When a non-conformity occurs, the following steps are needed to investigate and take actions for correction [28]:

1. The magnitude and scope of its risk should be assessed. If there is minimum risk, perhaps no further action is needed. Otherwise, a root cause analysis should be conducted to identify the assignable cause and a solution should be identified;
2. CAPA are taken to eliminate the root cause of the non-conformity and prevent its future occurrence;
3. The attribute associated with the non-conformance must be closely monitored to verify that it is now consistently in control and in specification.

For example, statistically evaluating analytical release data which may be within specification but trending low or increasing in total variability can result in the avoidance of an ultimate failure if the cause of variability can be discovered and rectified prior to it reaching a significant magnitude [24].

There are a multitude of SPC charting rules that may be useful to identify potentially statistically anomalous events. A common set of tests for special cause variation include, but are not limited to [26,51]:

- One point outside the upper or lower control limits;
- One point more than 3SD from the mean;

- Two out of three successive points more than 2SD from the mean on the same side of the center line;
- Four out of five successive points more than 1SD from the mean on the same side of the center line;
- Eight successive points on the same side of the center line;
- Nine sequential points on the same side of the mean;
- Six successive points increasing or decreasing (a trend);
- Fourteen sequential points alternate in direction (potential multiple underlying processes);
- Obvious cyclic behavior.

As explained in Chapter 2, Stage 3B allows detection of potential process failures. The product/process robustness monitoring is typically performed using SPC charts and automated notification of trends.

According to the Methodology presented in section 4.2, the results of the Batch Master Record analysis were obtained for the Product in question and the parameters corresponding to each stage of the process and also the IPC parameters were analyzed.

In theory, the **Process Performance Index, P_{pk}, is the most important one** because it shows how the process performed and how much variation the process exhibited, indicating how that variation will affect the ability of the process to meet the customer's requirements [34].

5.1 IPC Parameters (CQAs) data analysis

IPC parameters results are shown in Table 4 for Pareto analysis, control charts and Process Capability/Performance Indices.

Table 4- IPC parameters result for both dosages: Pareto analysis, control charts and Process Capability/Performance Indices.

Dosage	**IPC parameters (CQAs)**	**Pareto analysis** (batch)	C_{pk}	P_{pk}
1	**Average Mass**	#71	4.89	4.20
	Diameter	#9	0.75	0.51
	Disintegration	#13	4.86	4.80
	Friability	#8	2.23	1.98
	Hardness	#13	1.09	1.03
	Final Blend LOD	#3	0.33	0.33
	Granulate LOD*	#72	0.55	0.53
	Thickness	#4	1.73	1.09
2	**Average Mass**	#23	14.67	13.97
	Diameter*	#70	0.18	0.06
	Disintegration	#44	9.38	6.61
	Friability	#66	3.87	1.64
	Hardness*	#67	0.63	0.48
	Final Blend LOD*	#57	0.57	0.44
	Granulate LOD	#39	1.31	0.82
	Thickness*	#30	0.69	0.44

*In marked parameters, there are batches that are not within specification.

Note: The graphics generated in the software that allowed to draw the conclusions of Table 4, are represented in the **Annex II**.

Legend:

<0.66 **terrible**	0.67<**poor**<0.99	1.00<**marginally capable**<1.32	1.33<**capable**<1.66	1.67<**good**<1.99	>2.00 **excellent**

- **Dosage 1 - IPC parameters**

From **Pareto analysis**, it was observed that **#13 batch** is the one that repeat the most over the Pareto chart analysis for the IPC parameter, namely in Disintegration and Hardness parameter, so these batch was the one selected by the Pareto chart indicating that he had the most deviating value from the other batches and/or the specification limits.

From **control charts** in IPC parameters such as **Average Mass, Disintegration, Diameter, Friability, Hardness and Granulate LOD** it was not possible to identify potentially statistically anomalous events, which means those parameters are likely **in statistical control**. But IPC parameters such as **Thickness** has more than eight successive points on the same side of the center line which may be a sign of a statistical anomalous event. Also, **Final Blend LOD** parameter had more than one point more than 3SD from the mean.

From **Process Capability/Performance Indices Analysis**, IPC parameters such as **Average Mass, Disintegration and Friability have a normal distribution well centered**, with P_{pk}=4.20; P_{pk}=4.80; P_{pk}=1.98, respectively (P_{pk}>2.00 is considered excellent). On the other hand, IPC parameter such as **Diameter, Final Blend LOD and Granulate LOD have not a well centered distribution** because there were too many variations in the values, it corresponds to P_{pk}=0.51; P_{pk}=0.33; P_{pk}=0.53, respectively (P_{pk}<0.66 is considered terrible). There are also IPC parameters such as **Hardness and Thickness** that had low P_{pk} values but not terrible, as the mentioned ones above.

- **Dosage 2 - IPC parameters**

From **Pareto analysis**, it was observed that there was **no repetition of batches** in Pareto chart analysis for the IPC parameter of dosage 2 Medicine. Some batches had deviating values from the other ones and/or the specification limits.

From **control charts**, IPC parameters such as **Average Mass and Disintegration** it was not identified potentially statistically anomalous events, which means those parameters are **likely in statistical control**. But IPC parameters such as **Diameter, Hardness, Final Blend LOD and Thickness** have batches **Out of Specification**, also the last two referred parameters have more than one point more than 3SD from the mean, which can indicate a statistically anomalous event. **Friability** parameter had more than eight successive points on the same side of the center line and **Granulate LOD** parameter six successive points increasing or decreasing which indicates a possible Trend.

From **Process Capability/Performance Indices Analysis**, IPC parameters such as **Average Mass and Disintegration have a normal distribution well centered**, with P_{pk}=

13.97; P_{pk}= 6.61, respectively (P_{pk}>2.00 is considered excellent) and did not present significant variations between batch values. On the other hand, IPC parameters such as **Diameter, Hardness, Final Blend LOD, Granulate LOD and Thickness have not a well centered distribution** because there were too many variations in the values and the Process Performance Indices were too low, P_{pk}=0.06; P_{pk}=0.48; P_{pk}= 0.44; P_{pk}= 0.82; P_{pk}= 0.44 (P_{pk}<0.66 is considered terrible and 0.67<poor<0.99). Also, **Friability had an acceptable Ppk value**, P_{pk}=1.64 (1.33<capable<1.66).

5.2 Equipment parameters (CPPs) data analysis

For Equipment parameters the process steps considered were Granulation, Drying and Compression parameters.

5.2.1 Granulation

Results for the Granulation parameters, namely for Pareto analysis, control charts and Process Capability/Performance Indices are shown in Table 5.

Table 5- Equipment parameters (Granulation process step) results for both dosages: Pareto analysis, control charts and Process Capability/Performance Indices.

Dosage	**Equipment parameters (CPPs): Granulation**	**Equipment**	**Pareto analysis** (batch)	C_{pk}	P_{pk}
1	**Granulation end-point**	B	#73	0.80	0.55
	Granulation end-point	A	#8	1.44	0.42
	Peristaltic Pump Speed*	A	#71	0.89	0.20
2	**Granulation end-point**	B	#58	0.90	0.33
	Granulation end-point	A	#66	0.91	0.52
	Peristaltic Pump Speed	A	#68	0.73	0.27

*In marked parameter, there are batches that are not within specification.

Note: The graphics generated in the software that allowed to draw the conclusions of Table 5, are represented in the **Annex II**.

Legend:

<0.66 **terrible**	0.67<**poor**<0.99	1.00<**marginally capable**<1.32	1.33<**capable**<1.66	1.67<**good**<1.99	>2.00 **excellent**

- **Dosage 1 - Granulation parameters**

From **Pareto analysis**, it was observed that there was **no repetition of batches** in Pareto chart analysis. Some batches had deviating values from the other ones and/or the specification limits.

From **control charts**, in **Granulation end-point** parameter (**Equipment A and B**) it was not identified potentially statistically anomalous events, which means those parameters **may be in statistical control**. But, in case of **Peristaltic Pump Speed** parameter there were four OOS batches and eight successive points on the same side of the center line, and it can represent a statistically anomalous event.

From **Process Capability/Performance Indices Analysis**, all of analyzed parameters - **Granulation end-point (Equipment A and B) and Peristaltic Pump Speed** – had too many variations in the values which contributes to lower P_{pk} values which means that **all parameters had not a well centered distribution**, P_{pk}=0.55; P_{pk}= 0.42; P_{pk}= 0.20, respectively (P_{pk}<0.66 is considered terrible).

- **Dosage 2 - Granulation parameters**

From **Pareto analysis**, it was observed that there was **no repetition of batches** in Pareto chart analysis. Some batches had deviating values from the other ones and/or the specification limits.

From **control charts**, all analyzed parameters – **Granulation end-point (Equipment A and B) and Peristaltic Pump Speed – may not be in statistical** control. All parameters had more than eight successive points on the same side of the center line and it can contribute to statistically anomalous events.

From **Process Capability/Performance Indices Analysis**, all parameters - **Granulation end-point (Equipment A and B) and Peristaltic Pump Speed** – had too many variations in the values which contributes to lower P_{pk} values, which means that parameters had **not a well centered distribution**, with P_{pk}= 0.33; P_{pk}= 0.52; P_{pk}= 0.27, respectively (P_{pk}=<0.66 is considered terrible).

5.2.2 Drying

Drying parameters results are shown in Table 6 for Pareto analysis, control charts and Process Capability/Performance Indices.

Table 6- Equipment parameters (Drying process step) results for both dosages: Pareto analysis, control charts and Process Capability/Performance Indices.

Dosage	**Equipment parameters (CPPs): Drying**	**Equipment**	**Pareto analysis** (batch)	C_{pk}	P_{pk}
1	**Inlet Air Temperature**	C	#71	2.86	0.27
	Inlet Air Volume		#71	1.07	0.21
	Outlet Air Temperature*		#2	-0.07	-0.02
	Product Temperature*		#2	-0.39	-0.09
2	**Inlet Air Temperature**		#68	0.39	0.17
	Outlet Air Temperature		#67	0.36	0.17
	Product Temperature		#67	0.32	0.18

*In marked parameters, there are batches that are not within specification.

Note: The graphics generated in the software that allowed to draw the conclusions of Table 6, are represented in the **Annex II**.

Legend:

<0.66 **terrible**	0.67<**poor**<0.99	1.00<**marginally capable**<1.32	1.33<**capable**<1.66	1.67<**good**<1.99	>2.00 **excellent**

- **Dosage 1 - Drying parameters**

From **Pareto analysis**, it was observed that **#2 and #71 batches** were the ones selected by the Pareto chart indicating that they had the most deviating value from the other batches and/or the specification limits.

From **control charts**, all analyzed parameters – **Inlet Air Temperature, Inlet Air Volume, Outlet Air Temperature and Product Temperature – may not be in statistical control**. Inlet Air Temperature and Inlet Air Volume had more than eight successive points on the same side of the center line and in case of Outlet Air Temperature and Product Temperature, both had four OOS batches.

From **Process Capability/Performance Indices Analysis**, all of analyzed parameters – **Inlet Air Temperature, Inlet Air Volume, Outlet Air Temperature and Product Temperature –** had too many variations in the values which contributes to lower values meaning that **all parameters had not a well centered distribution**, with P_{pk}= 0.27; P_{pk}= 0.21; P_{pk}= -0.02; P_{pk}= -0.09, respectively (P_{pk}<0.66 is considered terrible).

- **Dosage 2 - Drying parameters**

From **Pareto analysis**, **#67 batch** was the one that repeat the most over the Pareto chart analysis, namely in Outlet Air Temperature and Product Temperature parameters, so is the one selected by the Pareto chart indicating that it had the most deviating value from the other batches and/or the specification limits.

From **control charts**, all dosage 2 Drying parameter - **Inlet Air Temperature, Outlet Air Temperature and Product Temperature – may not be in statistical control**. All of them had more than eight successive points on the same side of the center line and it can represent a statistically anomalous event. There was no OOS values by control charts observation.

From **Process Capability/Performance Indices Analysis**, although there were no OOS values by control charts observation, there were indeed too many variations in the values and all of them were too close from the LSL or USL, which means that all of analyzed parameters **– Inlet Air Temperature, Outlet Air Temperature and Product Temperature –** had lower values and all parameters had **not a well centered distribution**, with P_{pk}= 0.17; P_{pk}=0.17; P_{pk}=0.18, respectively (P_{pk}<0.66 is considered terrible).

5.2.3 Compression

Compression parameters results are shown in Table 7 for Pareto analysis, control charts and Process Capability/Performance Indices.

Table 7- Equipment parameters (Compression process step) results for both dosages: Pareto analysis, control charts and Process Capability/Performance Indices.

<table>
<tr><th>Dosage</th><th>Equipment parameters (CPPs): Compression</th><th>Equipment</th><th colspan="2">Pareto analysis (batch)</th><th colspan="2">C_{pk}</th><th colspan="2">P_{pk}</th></tr>
<tr><td rowspan="5">1</td><td>Pre-Compression Force</td><td rowspan="10">H</td><td colspan="2">#2</td><td colspan="2">0.43</td><td colspan="2">0.31</td></tr>
<tr><td>Compression Force</td><td colspan="2">#13</td><td colspan="2">0.68</td><td colspan="2">0.65</td></tr>
<tr><td>Fill Depth (maximum/minimum)</td><td>#73</td><td>#16</td><td>1.34</td><td>1.13</td><td>0.97</td><td>0.82</td></tr>
<tr><td>Output Rate</td><td colspan="2">#13</td><td colspan="2">0.69</td><td colspan="2">0.44</td></tr>
<tr><td>Feed Shoe Settings</td><td colspan="2">#1</td><td colspan="2">0.55</td><td colspan="2">0.52</td></tr>
<tr><td rowspan="5">2</td><td>Pre-Compression Force</td><td colspan="2">#64</td><td colspan="2">0.98</td><td colspan="2">0.43</td></tr>
<tr><td>Compression Force</td><td colspan="2">#24</td><td colspan="2">1.12</td><td colspan="2">0.58</td></tr>
<tr><td>Fill Depth (maximum/minimum)</td><td>#24</td><td>#59</td><td>2.37</td><td>1.25</td><td>1.27</td><td>0.78</td></tr>
<tr><td>Output Rate</td><td colspan="2">#29</td><td colspan="2">1.56</td><td colspan="2">0.95</td></tr>
<tr><td>Feed Shoe Settings</td><td colspan="2">#24</td><td colspan="2">0.73</td><td colspan="2">0.38</td></tr>
</table>

Note: The graphics generated in the software that allowed to draw the conclusions of Table 7, are represented in the **Annex II**.

Legend:

<0.66 **terrible**	0.67<**poor**<0.99	1.00<**marginally capable**<1.32	1.33<**capable**<1.66	1.67<**good**<1.99	>2.00 **excellent**

- **Dosage 1 – Compression parameters**

From **Pareto analysis**, it was observed that **#13 batch** was the one that repeat the most over the Pareto chart analysis for the Compression parameter, namely in Compression Force and Output Rate parameter, so is the one selected by the Pareto chart indicating that it had the most deviating value from the other batches and/or the specification limits.

From **control charts**, in **Compression Force, Fill Depth and Feed Shoe Settings** parameters were not identified potentially statistically anomalous events, which means those parameters **may be in statistical control**. In case of **Pre-Compression Force** parameter, it was detected one point more than 3SD from the mean, which **may indicate a statistically anomalous event**. Finally, in **Output Rate** parameter it was possible to observe more than eight successive points on the same side of the center line. No OOS batches were identified.

From **Process Capability/Performance Indices Analysis**, although there were no OOS batches by control charts observation, there were indeed too many variations in the values and all of them were too close to the LSL or USL, meaning that all of analyzed parameters, Pre-Compression Force, Compression Force, Fill Depth (maximum/minimum), Output Rate and Feed Shoe Settings had lower values and **all parameters had not a well centered distribution**, with P_{pk}= 0.31; P_{pk}=0.65; P_{pk}=0.97/0.82; P_{pk}= 0.44; P_{pk}=0.52 (P_{pk}<0.66 is considered terrible and 0.67<poor<0.99).

- **Dosage 2 - Compression parameters**

From **Pareto analysis**, it was observed that **#24 batch** was the one that repeat the most over the Pareto chart analysis for the Compression parameter, namely in Compression Force and Output Rate parameter, so is the one selected by the Pareto chart indicating that it had the most deviating value from the other batches and/or the specification limits.

From **control charts**, all dosage 2 Compression parameter – **Pre-Compression Force, Compression Force, Fill Depth, Output Rate and Feed Shoe Settings – may not be in statistical control**. The first four parameters had more than eight successive points on the same side of the center line and it can represent a statistically anomalous event. Also, Feed Shoe Settings had one point more than 3SD from the mean.

From **Process Capability/Performance Indices Analysis**, although there were no OOS values by control charts observation, there were indeed too many variations in the values and all of them were too close from the LSL or USL, which means that all of analyzed parameters, Pre-Compression Force, Compression Force, Fill Depth (maximum/minimum), and Feed Shoe Settings had lower values and **all parameters had not a well centered distribution**, with P_{pk}=0.43; P_{pk}= 0.58; P_{pk}=1.27/0.78; P_{pk}=0.38 (P_{pk}<0.66 is considered terrible and 0.67<poor<0.99). Only Output Rate value P_{pk}= 0.95 is considered marginally capable.

5.3 Factors that might had influence in OOS results

5.3.1 Control charts and Process Capability/Performance Indices observations: parameters not statistically controlled and OOS results

There are some main factors to consider that may have influence on Out of Specification results, i.e., factors that may have changed during the process that contributed to the results being OOS in several parameters. For this purpose, parameters with OOS batches were identified and the ones that were not in statistical control according to control charts observation and Process Capability/Performance Indices values were described.

According to ICH Q10 [9], the definition of State of Control is "A condition in which the set of controls **consistently** provides **assurance** of continued process performance and product quality" [46].

(1) Consistently- assessed using Statistical Process Control Charts;
(2) Assurance- assessed using the Process Capability Indices.

Ultimately trend analysis should not be defined by run/line charts and if Process Capability/Performance Indices are used, statistical control should be determined. Control charts and Process Capability/Performance Indices should be used together for effective verification of the state of control (an acceptable quality level) and a tool for process improvement [46].

It was observed that, in **IPC parameters** for **dosage 1**, the only one that was **not in Statistical Control is Final Blend LOD** parameter because both in control charts and Process Capability/Performance Indices it had more than one point more than 3SD from the mean and not a well centered distribution, respectively. For **dosage 2**, there are many parameters that are **not in Statistical Control such as Diameter, Hardness, Final Blend LOD, Granulate LOD and Thickness** (all of them had **OOS batches**, except from Granulate LOD parameter) because it was possible to identify potentials statistically anomalous events in control charts and had not a well centered distribution in Process Capability/Performance Indices graphics. So, in IPC parameters there is one of them that highlight from the others because in **both dosages, it is not in Statistical Control, which is Final Blend LOD**.

For **Equipment parameters**, in **Granulation** it was possible to observe that for **dosage 1**, the only parameter that was **not in Statistical Control is Peristaltic Pump Speed** (had **OOS batches**) because both in control charts and Process Capability/Performance Indices it had four OOS batches and eight successive points on the same side of the center line and not a well centered distribution, respectively. For **dosage 2**, **Granulation end-point (Equipment A and B) and Peristaltic Pump Speed parameters are not in Statistical Control** because it was possible to identify potentials statistically anomalous events in control charts and had not a well centered distribution in Process Capability/Performance Indices graphics. Also, Granulation end-point (Equipment A) had **OOS batches**. So, in Granulation Equipment parameters, **Peristaltic Pump Speed** highlights from the others because **in both dosages was not in Statistical Control**.

For **Drying Equipment parameters**, it was possible to observe that for **dosage 1**, **all of analyzed parameters Inlet Air Temperature, Inlet Air Volume, Outlet Air Temperature and Product Temperature were not in Statistical Control** (the last two parameters had **OOS batches**). For **dosage 2**, **all of analyzed parameters Inlet Air Temperature, Outlet Air Temperature and Product Temperature were not in Statistical Control either**. In all of referred parameters was possible to identify potentials statistically anomalous events in control charts and had not a well centered distribution in Process Capability/Performance Indices graphics.

For the last analyzed **Equipment parameters**, for **Compression**, it was possible to observe that for **dosage 1** there were two parameters that were **not in Statistical Control: Pre-Compression Force and Output Rate**. For **dosage 2**, all analyzed parameters **Pre-Compression Force, Compression Force, Fill Depth, Output Rate and Feed Shoe Settings were not in Statistical Control** because, similar to dosage 1, in both control charts and Process Capability/Performance Indices was possible to identify potentials statistically anomalous events and had not a well centered distribution, respectively. So, in Compression Equipment parameters, **Pre-Compression Force and Output Rate were not in Statistical Control** in both dosages and highlight from the others.

Drying and **Compression Equipment parameters** were the ones that had more parameters not statistically controlled, so these process steps are the more critical to evaluate in the manufacturing process.

Generally**, Equipment parameters (CPPs),** in all evaluated process steps- Granulation, Drying and Compression- **had less Statistical Control parameters compared to IPC parameters (CQAs)**. So, Equipment parameters might have more influence in changes in the process that leaded to OOS results in some batches.

5.3.2 Raw Materials Origin

According to PQRs and Batch Master Record as regards for each Medicine dosage, **no differences in the origin of the API or excipients have been identified** to justify variations in Out of Specification values.

5.4 Complaints analysis

The color of these Medicine is white to off-white, as the approved Marketing authorization. It was possible to observe the batches that presented complaints to the Company (Table 8) due to several reasons, being the one that stands out the **yellow aspect of some tablets within some batches** and, because of that, a worthy investigation is needed to discover what is going wrong in the manufacturing process.

A detailed complaints analysis for the chosen Medicine was done in order to understand what caused the change of an organoleptic property (color) in the tablet.

5.4.1 Ishikawa Diagram

An Ishikawa Diagram (Figure 11) was done to determine the causes of the yellowish tablet color. It is defined as a graphic representation that schematically illustrates the relations between a specific result and its causes. The studied effect or negative problem is “the fish head” and the potential causes and sub-causes define the “fish bone structure” [52,53].

Benefits of using an Ishikawa Diagram are to help determine root causes, use an orderly, easy-to-read format, indicate possible causes of variation, increase process knowledge, and identify areas for collecting data [52].

Causes are usually grouped into major categories to identify these sources of variation. The categories typically include [52]:

- **People**: Anyone involved with the process.
- **Methods**: How the process is performed and the specific requirements for doing it, such as policies, procedures, rules, regulations and laws.
- **Machines**: Any equipment, computers, tools, etc. required to accomplish the job.
- **Materials**: Materials used to produce the final product.
- **Measurements**: Data generated from the process that are used to evaluate its quality.
- **Environment**: The conditions in which the process operated.

Table 8- Complaints Analysis: Cause(s) and Implemented Solutions by Generis® in Production – Both dosages.

Dosage	Batch	Complaint Description	Root-Cause	Implemented Solution
1	#10	**Absence of one tablet in the blister**, half of a tablet instead of one complete tablet	Human error	No corrective or preventive measures were considered
2	#18	**Scratch** when swallowing	Related to compression tools	New compression tools were purchased for the Medicine tablets
	#32	One tablet has a **black powdery residue**	Dust particles mixed with the oil from the lubrication of the compression machine punches	As a preventive measure, the need to exchange the retainers between each compressed batch was established
	#41	Some tablets have a **different color** (yellow)	API is a photosensitive substance, which oxidizes easily in light and gives rise to a yellowish color	Measures are under evaluation
	#47			
	#48			
	#49			
	#50			
	#51			
	#52			
	#53			

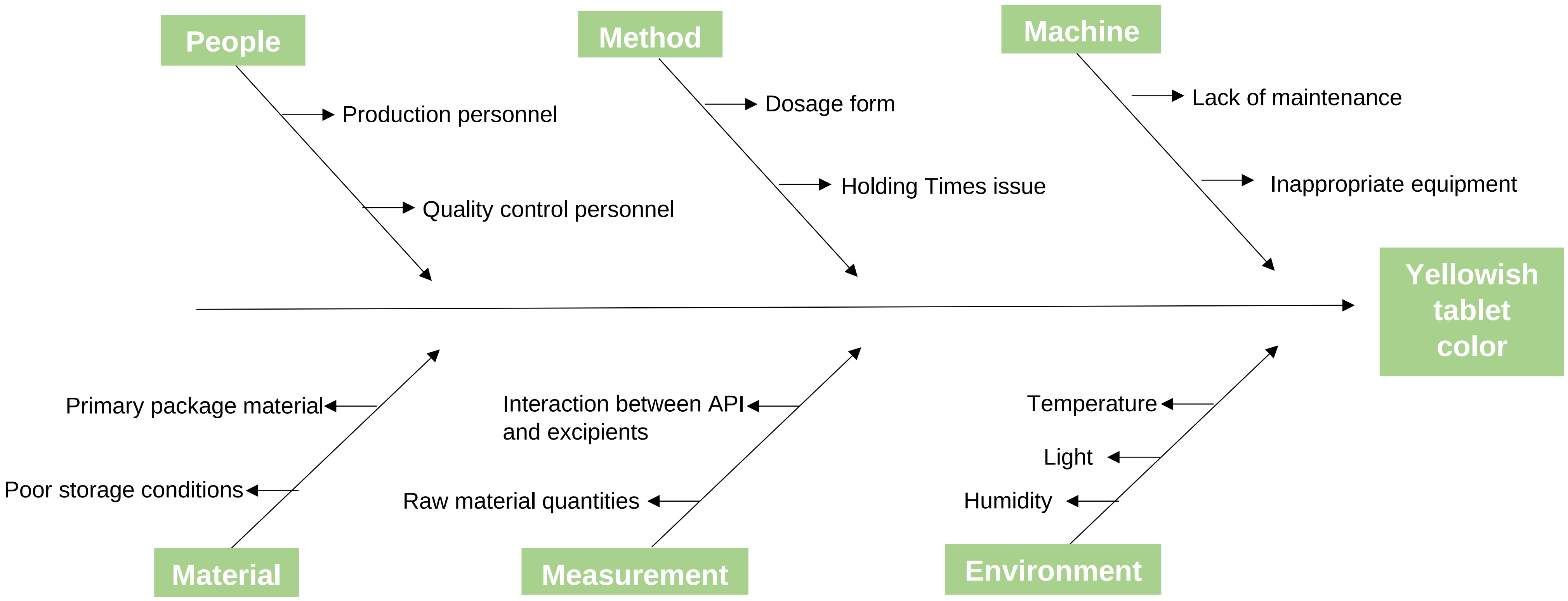


Figure 11- Ishikawa Diagram: Yellowish tablet color.

5.4.2 Causes worth investigation for Yellowish Tablet Color

The quality of pharmaceutical products is affected by many factors, such as the stability of the APIs potential interaction between active(s) components and excipients, manufacturing process, dosage form, packaging system, environmental conditions encountered during transport, storage and use and length of time between manufacture and usage [54].

Complaints for the Medicine in question were reviewed to understand the main reason for the yellowish color the tablet has sometimes in few tablets when distributed to the public and the need to solve it. After doing the Ishikawa diagram, it was possible to understand some causes of the problem for yellowish tablet color (color changed).

One of the possible solutions to the problem under investigation focuses on the **Holding Times** and whether it has an influence on the color change of the tablet. Other solutions under investigation are the **primary packaging material**, **poor storage conditions**, and **dosage form**.

The Medicine under study has the following **components**:

- ✓ API;
- ✓ Monohydrate lactose;
- ✓ Cellulose MC;
- ✓ Povidone (PVP);
- ✓ Crospovidone;
- ✓ Silicon Colloidal;
- ✓ Stearic Acid;
- ✓ Water.

- **Holding Times –** can be considered as the established time period for which materials (dispensed raw materials, intermediates and bulk dosage form awaiting final packaging) may be held under specified conditions and will remain within the defined specifications [55].

GMP require that arrangements should be made to ensure that the dispensed raw materials and packaging materials, intermediate products, bulk and finished products are stored under appropriate conditions. Storage arrangements should not have deleterious effects on the subsequent processing, stability, safety, efficacy or quality of starting materials, intermediate products and bulk products prior to final packaging. Maximum acceptable holing periods should therefore be established to ensure that intermediates and bulk product can be held without producing results outside the acceptance criteria for the quality of the material.

Commonly, intermediate and bulk products should not be stored beyond the established hold time [55].

This practice is supported by indirect references made to determining Holding Times in various FDA regulations as follows [56,57]:

- "If a firm plans to hold bulk medicine products in storage… stability data should be provided to demonstrate that extended storage in the described containers does not adversely affect the dosage".
- "Stability data also may be necessary when the finished dosage form is stored in interim containers prior to filling into the marketed package. If the dosage form is stored in bulk containers for over 30 days, real-time stability data under specified conditions should be generated to demonstrate comparable stability to the dosage form in the marketed package. Interim storage of the dosage form in bulk containers should generally not exceed six months".
- "When appropriate, time limits for the completion of each phase of production shall be established to assure the quality of the drug product". This regulation could be interpreted to include the time for holding bulk product as part of the production process. "Holding Times (includes storage times) studies may be conducted during development or carried out in conjunction with Process Validation lots and shall be representative of full-scale holding conditions".

In Table 9 are represented the Hold Time study requirements for Solid Oral Forms and the required tests in each operation unit [58].

Table 9- Hold Time study requirements for Solid Oral Forms [58].

Un-Coated Tablets	Hold Time study points (day)	Tests required
Dry Mixing	7, 15 and 30	Description, LOD or water content
Binder solution	Initial, 1/2, 1, 1 and 1/2, 2 and 3	Description
Wet Granules	Initial, 1/2, 1, 1 and 1/2, 2 and 3	Description, LOD or water content and assay
Blending	7, 15, 30, 45 and 60	Description, LOD or water content and assay
Un-coated Tablets	7, 15, 30, 45 and 60	Description, LOD or water content, assay, and dissolution

Typically, bulk tablets and capsules may be held for up to 30 days from their date of production without being retested prior to use. A bulk product that is held for longer than 30 day should be monitored for stability under controlled, long-term storage conditions for the length of the holding period. Interim storage of the dosage form in bulk containers should generally not exceed six months. At the test points, a sample should be taken from the storage container and tested. Results obtained should be compared with the initial baseline data of the tablet/capsule control sample results [56].

The choice of maximum holding period should be supported by relevant data. Studies may extend beyond the chosen maximum, but it is not necessary to extend testing to determine the extreme limits at which failure occurs [55].

- **Primary packaging material –** Primary packaging material refers to a packaging component that is or may be in direct contact with the dosage form [59].

The choice of the container materials for any particular tablet product must be done only after a thorough evaluation of the influence of these materials on the stability of the product and the effectiveness of the container in protecting the product during extended storage under varying environmental conditions of temperature, humidity, and light [60].

Products are always packaged in containers for storage and marketing for convenience of handling, use and product protection. Stability information of a product in selected containers regarding the proposed shelf life is part of the quality information required to obtain approval from regulatory agencies to market any product, in addition to proof that the product is safe, efficacious, high quality, and made in compliance with current good manufacturing practices [61].

- **Poor storage conditions –** The knowledge of the various storage conditions for individual products and the need to provide such optimal storage conditions is therefore of prime importance [54].

According to a study [62] into the stability, the undertaking of parallel physical parameters as well as the dissolution studies of the storage tablets, it was found that, **the color of the tablets stored at 40ºC/75% RH was slightly changed from off white to heavy off white at the end of the period of study, for PVC/Alu blisters**.

For both dosages of this Medicine, the used blister is in PVC/PVDC 250µm/60g/m^2 transparent (formation material) and Alu 20µm (covering material).

According to another study [54], it was concluded that the excipient povidone (**PVP**) **when exposed to light, can cause changes in the properties of the tablet** (**depending on the**

storage time and conditions). This may be related to moisture loss in the powder as a result of heat energy from the sun. Since the **product in question has PVP in its composition**, this may be a possible route of study on the color change of the tablet.

- **Dosage form –** According to Table 8 the dosage form that had more complaints is **dosage 2**, particularly in the case of the yellowish aspect, where it was the only dosage that presented that problem.

5.4.3 Considerations

Comparing complaints analysis with OOS batches in Results analysis, it was possible to analyze that **five of the mentioned batches** (#47, #49, #50, #52, #53) in Table 8 are batches that were **Out of Specification in Diameter IPC parameter**. None of other batches in Table 8 had OOS values in any analyzed parameters. Diameter has no direct relationship with organoleptic properties (tablet color).

A very important point worthy investigation is that the **API** is not the only one that is a photosensitive substance and oxidizes when exposed to light and also, **povidone**, PVP, have those properties too and that **can lead to color changes in the tablet**.

Dosage form was another important aspect to be considered, as dosage 2 was **the only one that had complaints about the color change of the tablet** (yellowish aspect). But, the percentage (%) of API and PVP excipient (photosensitive ones) used is the same in both dosages.

In fact, many factors can lead to color change in the tablet. **Solutions may include protective barriers implementation, for reducing exposure to light during manufacture, changing packaging material and Holding Times studies may also be needed**.

5.5 Low Yield Problem

To analyze and identify the defects in the process and find the causes to Low Yield (below defined specification) Problem, it was important to understand at which stage of the process the most significant process losses occurred.

In Table 10 were described how many batches had low yield values, the process step in which it occurred and the total number of analyzed batches, to compare between the two Medicine dosages and understand what dosage had more batches with low yield.

According to Table 10, the most critical stage with low yield values was the **Compression Process Step** which subsequently affects the Final Yield values – **38 batches below specification due to compression losses**, which corresponds to 10 batches of dosage 1 and 28 batches of dosage 2.

Table 10- Number of Batches with Low Yield- Both dosages.

Dosage	Batches with Low Yield	Process Step	Total number of analyzed batches
1	9	Compression	20
	1	Final Blend and Compression	
2	26	Compression	53
	2	Final Blend	
	4	Losses during the process	
	2	Final Blend and Compression	

In terms of percentage, **dosage 2** had more Low Yield batches than **dosage 1**, mainly in Compression Process Step, 57% and 50% respectively, which means that dosage 2 had more OOS results, below the Yield specification. This contributed to investigate Compression Losses causes. As referred before (section 5.3.1) Equipment parameters need more attention to possible changes/improvements than IPC parameters, since the main problem identified of Low Yield Problem was effectively Compression Losses.

5.5.1 Compression Losses

According to Batch Master Records, the low yield problem focuses mainly on **Compression Losses** (Setup and Suction). Rotary tableting machines are used for compression.

Compression of tablets include the general term tabletability, comprising, compressibility and compactibility [63].

Tabletability is the ability to form tablets of certain properties under pressure. It is often expressed as the tensile strength of the tablets as a function of the tableting pressure. As a consequence, in order to follow the tablet formulation in more detail, volume reduction versus time (compressibility) needs to be quantified [63].

For a quantitative description of the tableting event, accurate time-resolved force and displacement data are necessary. The significance of data inaccuracy on parameterization has been frequently discussed concerning to the reproducibility (intra-laboratory precision) and repeatability (inter-laboratory precision) [63].

A high-speed rotary tablet press can be fine-tuned by a well-considered selection of feed frame design at its most optimal process settings. As the role of the rotary tablet press in a continuous tableting manufacturing line is steadily evolving towards a more agile unit-operation, capable of handling fluctuations in the upstream material flow, it becomes increasingly important to have more knowledge on how the feed frame design and process-settings such as tableting speed, paddle speed and overfill level might influence the tableting process [64].

Rotary presses are used for high volume production, of the order of 100 000-500 000 tablets per hour. The central component of a rotary press is a round die table with a number of tooling stations, which consist of upper punch-die-lower punch assemblies. Nearly all production of pharmaceutical tablets nowadays takes place on these presses. The die and punches reside in a rotating turret and pass through the filling station, precompression and main compression rollers and the ejection station [65].

On rotary tablet presses, the compression process generally consists out of two compression steps, pre- and main compression. At precompression a lower force is applied, mainly with the aim of removing excess of air present between the powder particles. Even so, with a precompression step the total time the powder is compressed is prolonged, contributing to stronger tablets [65].

Although seemingly simple, compression on a rotary tablet press is a complicated engineering process, as a large amount of process parameters can be varied, irrespective of the press and tooling set, in contrast to an eccentric tablet press. The compression step can be influenced by both the position of the upper and lower roller, as the distance between them controls the thickness and hence the compression force. Furthermore, their position relatively to the die table determines the indie compression position, from which is known to influence the final tablet characteristics [65].

Nowadays, there are strong incentives for an increased understanding of material properties and pharmaceutical manufacturing processes: **in-line monitoring and analysis of pharmaceutical process are aimed at better process control and control of end-product quality** [63].

5.5.2 Considerations

Even when using multivariate statistical approaches, it cannot be expected to find a global evaluation method that fully explains the mechanism of tableting, but that careful sequential evaluation is required. For further improvement, there is a need to use more complex models and alternative technologies, in order to increase both tablet quality and productivity [63].

Due to the large number of process parameters that can be varied and their interactions, a rational and structural approach is necessary for conducting experiments which provide the maximum amount of relevant information (about the process parameters, their relation to each other and their influence on the product attributes), in the most efficient way. **DoE** is an approach in which the controlled input factors of the process are systemically (and simultaneously) varied in order to obtain the maximum of information, with only a limited number of experiments. The effects on the output variables and the most influential factors can be identified. DoE has a mathematical foundation behind the experimental procedures and yields the maximum information for a given amount of data. Moreover, this approach not only allows to investigate the experimental space (i.e., the area which spans the parameter ranges from which information needs to be gathered) in a structured way (screening) but also to make found decisions on which values the factors should have to ensure that the response is close to the target value (optimization) with a minimum of uncertainty (robustness). Consequently, the final process design space can be defined, as the multi-dimensional combination and interaction of input variables and process parameters that have demonstrated to provide quality assurance [65].

As to the concepts of QbD and PAT, in the case of tableting, there is a demand on the characterization of the materials (excipients) in terms of critical properties and steps of the tableting process and to the performance of the tablet in a risk analysis-based approach. These approaches have found their consequence in the regulatory guidelines for drug products in general, for example, in ICH Q8 Pharmaceutical Development [63].

Noninvasive spectroscopic methods, such as **Near-infrared Spectroscopy (NIR) and Raman**, have proven to be useful tools to study consistency of raw materials. Multivariate models reflecting the acceptable variation in basic powder properties of raw materials for a product can contribute to ensure a robust process which are, in this case, **the tableting step and tablet mechanical properties** [63].

A mechanistic understanding of the structure of the materials, basic properties and the effect of processing is necessary for meaningful **use of DoE and PAT as formulation and process optimization tools**. For the analysis of direct compression processes, physical and physicochemical approaches to characterize the input materials (i.e., functional-related properties such as particle size, powder flow, and others), the process data (i.e., time-resolved force and displacement data and derived parameters) and the properties of the final product (i.e., tablet tensile strength, drug release, and others) are combined [63].

The compression step of a single, crystalline and well-characterized material (i.e., in terms of particle size, particle size distribution, particle shape, surface properties) is a particular fast and complex process compared with other pharmaceutical production processes. The current developments in the fields of sensors and computing will have large impact on the data quality in the nearest future. However, this may not solve the problem of a thorough description of the compression event, because tablets are not homogenous nor continuous, and particle properties depend on many other parameters, such as shape, orientation and pre-experienced stress [63].

The benefit of multivariate designs is to cover many more parameters in the same models. However, if they should be extended to predictive abilities, a more thorough understanding of the physical processes is still needed. For such mechanism-based evaluation of the contribution of the materials, sequential handling of different approaches will be useful based on the physical processes that are involved in order to single out the different overlapping effects [63].

6 OPV Protocol

An OPV protocol was developed specially for the Company to implement an OPV Program and is represented below. It is new for the company and an added value for the improvement of the process.

OPV PROTOCOL

Title: Ongoing Process Verification Protocol

Index

1. Purpose

Demonstrate with a high degree of confidence and through appropriate data documentation and analysis, that the OPV program needs/not need to be implemented, through statistical analysis of medicines data, in accordance with monitoring of critical process and quality parameters. The aim will be to check if that the manufacturing process is consistent, reproducible, under control and capable of ensuring the manufacture of a product that meets all analytical specifications and quality attributes.

2. Scope

Applicable to Medicine (dosages 1 and 2) manufacturing process and to the following areas: Quality Assurance, Quality Control and Production.

3. Definitions and Abbreviations

Control Strategy	A planned set of controls, derived from current product and process understanding that ensures Process Capability and product quality. The controls can include parameters and attributes related to active substance and finished product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control.
Critical Process Parameter	A process parameter whose variability has an impact on a Critical Quality Attribute and therefore should be monitored or controlled to ensure the process produces the desired quality (ICH Q8).
Critical Quality Attribute	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 (ICH Q8).
Process Capability Index (C_{pk})	Potential of a process to meet a specification (short term), used to determine the efficiency of the process.
Process Capability Index (P_{pk})	Incorporates information about both the process spread and the process mean and so is a measure of how the process is performing. How the process actually did (long term).
CS	Control Strategy
OPV	Ongoing Process Verification
PD	Production

QA	Quality Assurance
QC	Quality Control

4. Documents Associated

VN IF PD	Batch Master Record of the Medicine
PQR	Product Quality Review
EMA	EU Guideline for Good Manufacturing Practice- Annex 15: Qualification and Validation; ICH Q8, Q9, Q10

5. Product Information

Medicine with two dosages (dosages 1 and 2).

6. Personnel, roles and responsibilities

6.1 Quality Assurance (QA)

Ensuring training in all procedures associated.

Monitoring of operation, ensuring compliance with good practice reflected in the procedures in force and following the approved protocol.

Evaluate the parameters used during the operation as well as results obtained by the PD and QC.

Review periodically OPV extent and frequency.

Data analysis: collect data and statistical analysis.

Modify the requirements taking into account the current level of process understanding and process performance.

Approve the OPV protocol and corresponding report.

6.2 Production (PD)

Verification of the protocol.

Collect data.

Ensuring compliance with good practice reflected in current procedures and follow up the approved protocol. Ensure the follow up established parameters and the sampling plan set. Report any deviations that occur during the process to QA.

6.3 Quality Control (QC)

Collect data.

Verification of protocols, availability of analytical data and verification of its reports.

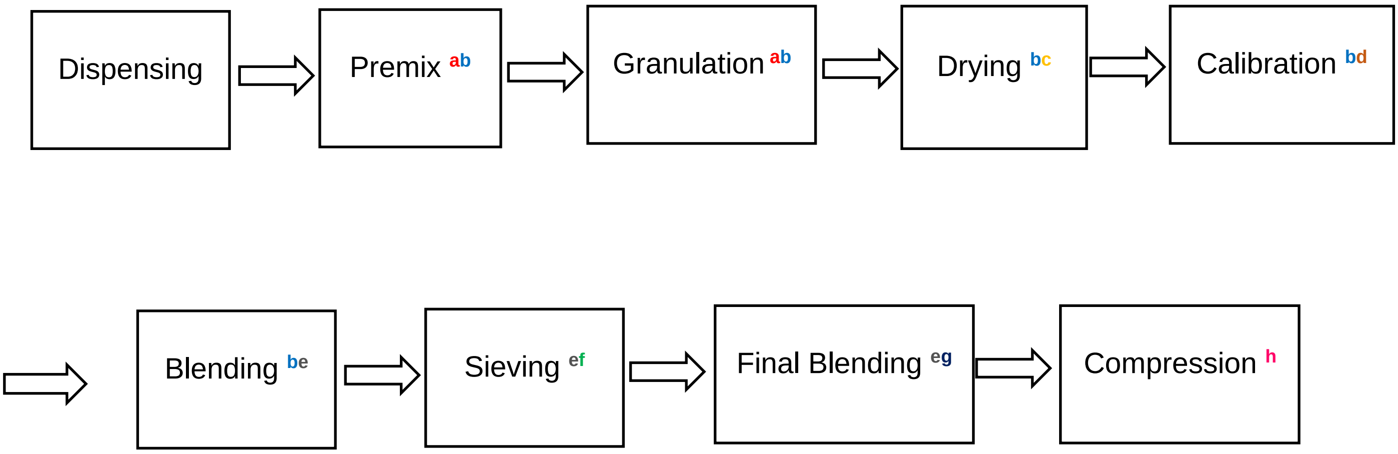
6.4 Qualified person

Regular analysis of results.

Control Strategy.

7. Procedure

7.1 Flowchart



Legend:

[a] Equipment A

[b] Equipment B

[c] Equipment C

[d] Equipment D

[e] Equipment E

[f] Equipment F

[g] Equipment G

[h] Equipment H

7.2 Raw Materials

Code	Designation	Batch
API		
	API	
Excipients		
	Monohydrate lactose	
	Povidone (PVP)	
	Crospovidone	
	Silicon Colloidal	
	Stearic acid	
	Water	

7.3 Equipment

Equipment	Model	Code	Process step
A	-		Mixture/Granulation
C	-		Drying
D	-		Calibration
F	-		Calibration
E	-		Mixture
G	-		Mixture
H	-		Compression
Granulation-Drying-Sieving B	-		Mixture/Granulation/Drying

8. Manufacturing process stages/Monitoring parameters

8.1 Granulation

Control Parameters	Equipment	Unit	Batch
Granulation end-point	A	Nm	
Granulation end-point	B	A	
Peristaltic Pump Speed	A	rpm	

8.2 Drying

Control Parameters	Equipment	Unit	Batch
Inlet Air Temperature	C	ºC	
Outlet Air Temperature	C	ºC	
Product Temperature	C	ºC	
Inlet Air Volume	C	m^3/h	

8.3 Compression

Control Parameters	Equipment	Unit	Batch
Pre-Compression Force	H	kN	
Compression Force	H	kN	
Fill Depth	H	mm	
Output Rate	H	un/h	
Feed shoe settings	H	rpm	

8.4 IPC parameters

Control Parameters	Unit	Batch
Granulate LOD	%	
Final Blend LOD	%	
Average Mass	mg/tab	
Disintegration Time	min	
Diameter	mm	
Friability	%	
Hardness	N	
Thickness	mm	

9. Software

Statgraphics® centurion XVI software was chosen to generate graphics that could help the statistically data analysis of the parameters data. This software has made it possible to use statistical tools useful for data analysis, such as Pareto charts, control charts and Process Capability/Performance Indices. The data is entered into the software in the form of an Excel® file and it is possible to handle the entered data according to the tools wished to use.

10. Process Deviations

Some batches had deviating values, i.e., Out of Specification in some parameters. In the case of dosage 1, in the granulation equipment parameters, the **Peristaltic Pump Speed** parameter had two Out of Specification batches. Still in dosage 1, in the Drying Equipment parameters, both **Outlet Air Temperature** and **Product Temperature** parameters had two Out of Specification batches each.

In the case of dosage 2, in IPC parameters, the **Diameter, Hardness, Final Blend LOD and Thickness** had OOS batches, 17, three, two and two, respectively. In the granulation equipment parameters, the **Granulation end-point** parameter (Equipment A) had one OOS batch.

11. Conclusions

Through results analysis, parameters with Out of Specification (OOS) results or low Process Capability/Performance Indices values were identified. Control charts and Process Capability/Performance Indices should be used together for effective verification of the process state of control. In IPC parameters, **Final Blend LOD** was identified as the most critical parameter because it was not in statistical control according to control charts and Process Capability/Performance Indices: $P_{pk\ (dosage\ 1)} = 0.33$; $P_{pk\ (dosage\ 2)} = 0.44$ ($P_{pk}<0.66$ is considered terrible). In Equipment parameters, for Granulation, **Peristaltic Pump Speed** was identified as the most critical parameter (not in statistical control) and, also, $P_{pk\ (dosage\ 1)} = 0.20$; $P_{pk\ (dosage\ 2)} = 0.27$. For Drying, **Inlet Air Temperature, Inlet Air Volume, Outlet Air Temperature** and **Product Temperature** parameters were not statistical controlled, also, for all parameters $P_{pk}<0.66$ in both dosages. For Compression, **Pre-Compression Force** and **Output Rate** parameters were the ones not in statistical control and with a $P_{pk}<0.66$.

7 Final considerations

7.1 Conclusions

This Master's thesis intended to contribute to the **design and implementation of an OPV program in a manufacturing process**, establishing a methodology on how to implement it and to design a protocol based on a critical evaluation of the manufacturing process for a Medicine (solid oral form, tablet). This methodology, as OPV Protocol, can be implemented for any medicinal product, using the data of the respective ones to be analyzed.

Through results analysis, parameters with Out of Specification (OOS) results or low Process Capability/Performance Indices values were identified. Control charts and Process Capability/Performance Indices should be used together for effective verification of the process state of control. In IPC parameters, **Final Blend LOD** was identified as the most critical parameter because it was not in statistical control according to control charts and Process Capability/Performance Indices: $P_{pk\ (dosage\ 1)} = 0.33$; $P_{pk\ (dosage\ 2)} = 0.44$ ($P_{pk}<0.66$ is considered terrible). In Equipment parameters, for Granulation, **Peristaltic Pump Speed** was identified as the most critical parameter (not in statistical control) and, also, $P_{pk\ (dosage\ 1)} = 0.20$; $P_{pk\ (dosage\ 2)} = 0.27$. For Drying, **Inlet Air Temperature, Inlet Air Volume, Outlet Air Temperature** and **Product Temperature** parameters were not statistical controlled, also, for all parameters $P_{pk}<0.66$ in both dosages. For Compression, **Pre-Compression Force** and **Output Rate** parameters were the ones not in statistical control and with a $P_{pk}<0.66$.

With regard to factors that have influenced OOS results, it should be noted that Equipment parameters were considered to have more influence in changes in the process that leaded to OOS values compared to the IPC ones. Although during the manufacturing process there have been OOS results and low Process Capability/Performance Indices, Drying and Compression parameters were the ones that had less statistically controlled Equipment parameters, being the most critical process steps, which means that Drying and Compression Equipment parameters had more deviation values.

According to complaints analysis, the major identified problem was the "yellowish tablet color" in some tablets. Five batches that had complaints were the same batches had OOS results in Diameter parameter, but no direct relationship was found with organoleptic properties. On the other hand, dosage 2 was the only one that had complaints about the color change of the tablet. An important consideration was, in fact, that **API and one of the excipients (PVP) are photosensitive and oxidize when exposed to light**.

From Low Yield Problem chapter, was concluded that **compression losses were the main responsible for that problem**. The number of batches with Low Yield were identified and it was proven that dosage 2 had more Low Yield (below the Yield specification) batches than dosage 1, 57% and 50%, respectively.

The defined measures, after identification of the process variability and the main problems after that, were:

- Concerning to process variability, parameters referred above should be reviewed, such as resetting specification ranges for those parameters that influenced the OOS results;

- As for the color change of the tablet for a yellowish appearance, solutions may include protective barriers implementation, for reducing exposure to light during manufacture, changing packaging material and Holding Times studies may also be needed;

- As for compression losses, compression machines may be evaluated and then, if there will not be identified any problem with the equipment or the process, QbD tools may be applied.

Once the variability of the process and the measures that could serve as the solution were identified, the next step, by the Company is to implement the measures and a well-structured OPV program, according to the defined methodology and OPV Protocol. Such as mentioned before, the implementation of this methodology will improve the performance of the manufacturing process, detect process variability before it becomes critical and help the company to identify failures and solve some of the problems detected.

7.2 Future work

- **Compression Losses**

Design of Experiments (DoE) provides a suitable tool for modeling the process and finding the optimal design space for robust tablet production. The use of soft sensors and in-line spectroscopy allows one to control and adjust the production to minimize process and quality variability [66].

Under the Quality by Design (QbD) for generic medicines, the effects of raw materials including both drug substance and excipients, and process parameters on the product quality are well understood. This means that manufacturers have knowledge of the operating range as well as the proven range of critical raw material attributes and process parameters. The operating range is defined as the upper and/or lower limits for raw material attributes and process parameter values between which the attribute and parameter are routinely controlled during production to assure reproducibility. The proven range can be established based on historical and/or experimental data. It can also be established based on scientific and operational judgement and expertise [33]. Within the QbD, design space is defined as the multidimensional combination and interaction of input variables and process parameters that have been demonstrated to provide quality assurance. The design space for generic medicines is likely established at small scale batches using Design of Experiments and prior knowledge, and may need to verified at commercial scale [33].

Understanding and implementing QbD will enhance and modernize the regulation of pharmaceutical manufacturing and product quality [33]. **In-line spectroscopy process analytical tools can be utilized for OPV**, building in redundancy for process modeling (i.e. to prove the validity of process models or to mitigate their potential integration issues), gathering additional information during manufacturing, measuring in-process controls, enabling multivariate Statistical Process Control and ultimately Real-Time Release Testing (RTRT). In a direct compression line, Process Analytical Technology (PAT) can be implemented to measure blend uniformity in the blender outlet stream or tablet press feed frame, or content uniformity after tablet compression [67].

This solution suggested above requires more investment and, despite its high efficiency, is considered to be of **high cost to the Company**.

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Annex I – Intermediate Graph Decision Tables

Table 11- Intermediate graph decision for Granulation (dosage 1).

Process Step	Dosage	Equipment	Equipment Parameters	Generate graphics	Problem
Granulation	1	A	Mixing Time	No	Several steps that cannot be evaluated
			Mixer Speed	No	Several steps that cannot be evaluated
			Granulator Speed	No	Several steps that cannot be evaluated
			Solution Addition Time	No	Have only a range of values
			Peristaltic Pump Speed	Yes	-
			Granulation end-point	Yes	-
		B	Mixing Time	No	Several steps that cannot be evaluated
			Mixer Speed	No	Several steps that cannot be evaluated
			Granulator Speed	No	Several steps that cannot be evaluated
			Solution Addition Time	No	Have only a range of values
			Peristaltic Pump Speed	No	Have only a range of values
			Granulation end-point	Yes	-

Table 12- Intermediate graph decision for Granulation (dosage 2).

Process Step	Dosage	Equipment	Equipment Parameters	Generate graphics	Problem
Granulation	2	A	Mixing Time	No	Several steps that cannot be evaluated
			Mixer Speed	No	Several steps that cannot be evaluated
			Granulator Speed	No	Several steps that cannot be evaluated
			Solution Addition Time	No	Have only a range of values
			Peristaltic Pump Speed	Yes	-
			Granulation end-point	Yes	-
		B	Mixing Time	No	Several steps that cannot be evaluated
			Mixer Speed	No	Several steps that cannot be evaluated
			Granulator Speed	No	Several steps that cannot be evaluated
			Solution Addition Time	No	Have only a range of values
			Peristaltic Pump Speed	No	Have only a range of values
			Granulation end-point	Yes	-

Table 13- Intermediate graph decision for Drying (dosage 1).

Process Step	Dosage	Equipment	Equipment Parameters	Generate graphics	Problem
Drying	1	C	Inlet Air Temperature	Yes	-
			Outlet Air Temperature	Yes	-
			Product Temperature	Yes	-
			Inlet Air Volume	Yes	-
		B	Inlet Air Temperature	No	Have only a range of values
			Inlet Air Volume	No	Have only a range of values
			Dehumidify	No	Have only a range of values
			Drying Time	No	Have only a range of values

Table 14- Intermediate graph decision for Drying (dosage 2).

Process Step	Dosage	Equipment	Equipment Parameters	Generate graphics	Problem
Drying	2	C	Inlet Air Temperature	Yes	-
			Outlet Air Temperature	Yes	-
			Product Temperature	Yes	-
			Inlet Air Volume	No	The same value in every batch
		B	Inlet Air Temperature	No	Have only a range of values
			Inlet Air Volume	No	Have only a range of values
			Dehumidify	No	Have only a range of values
			Drying Time	No	Have only a range of values

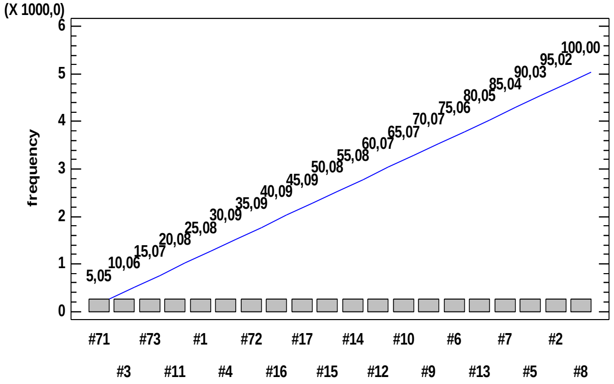
Table 15- Intermediate graph decision for Final Blending (both dosages).

Process Step	Dosage	Equipment	Equipment Parameters	Generate graphics	Problem
Final Blending	1	E or G	Mixing Time	No	The same value in every batch
			Mixer Speed	No	The same value in every batch
	2	E or G	Mixing Time	No	The same value in every batch
			Mixer Speed	No	The same value in every batch

Annex II – Graphics for IPC and Equipment Parameters Analysis

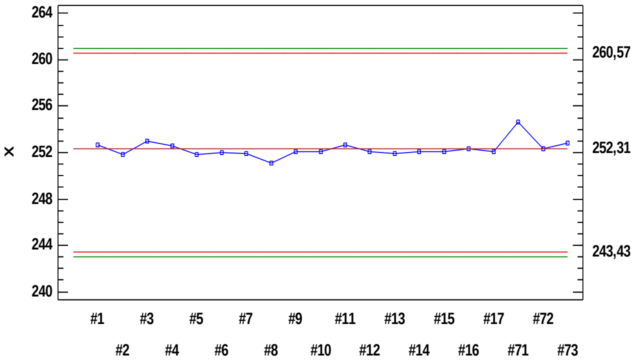
- **IPC parameters** graphics for **dosage 1**

A- Pareto chart for Average Mass (mg/tab).

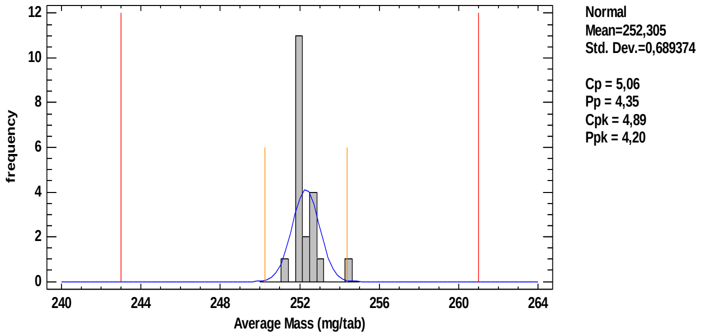


B- Control chart for Average Mass (mg/tab).

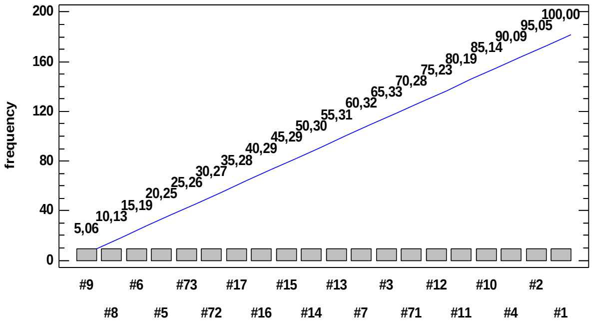
LSL = 243,0; USL = 261,0



C- Process Capability/Performance Indices for Average Mass (mg/tab).

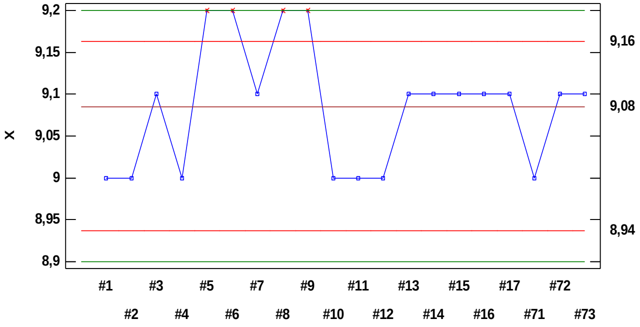


D- Pareto chart for Diameter (mm).

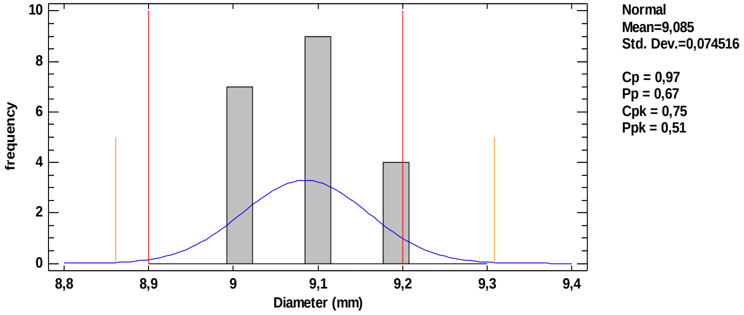


E- Control chart for Diameter (mm).

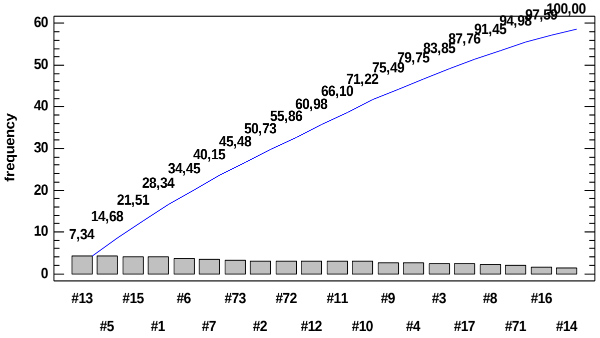
LSL = 8,9; USL = 9,2



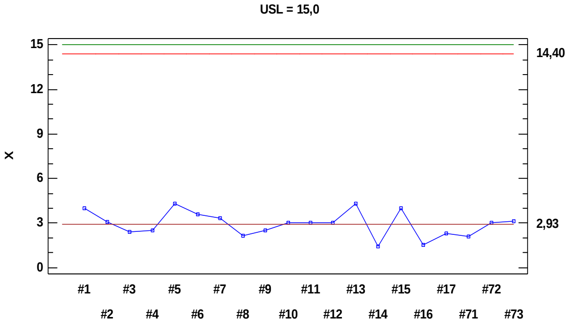
F- Process Capability/Performance Indices for Diameter (mm).



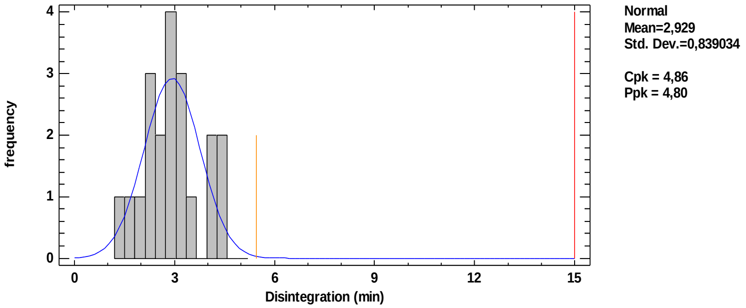
G- Pareto chart for Disintegration (min).



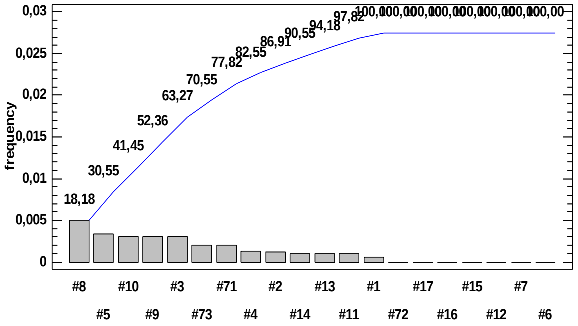
H- Control chart for Disintegration (min).



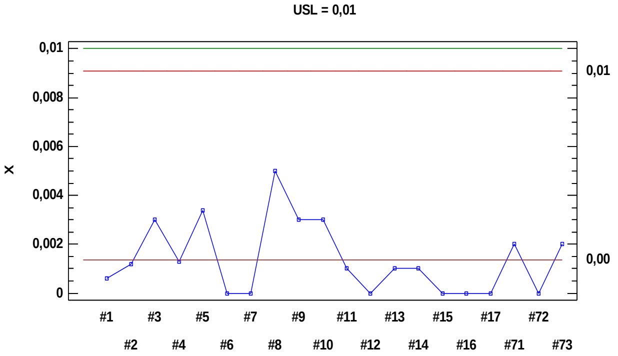
I- Process Capability/Performance Indices for Disintegration (min).



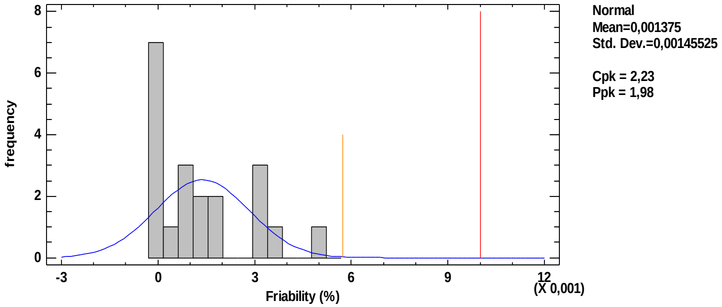
J- Pareto chart for Friability (%).



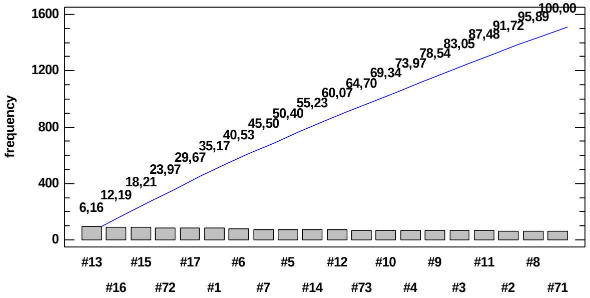
K- Control chart for Friability (%).



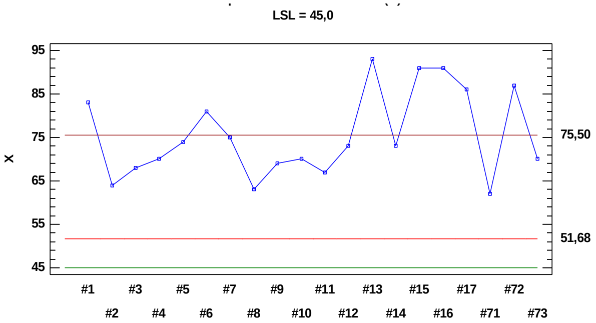
L- Process Capability/Performance Indices for Friability (%).



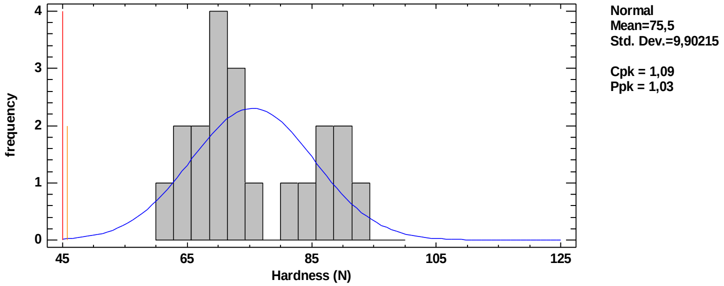
M- Pareto chart for Hardness (N).



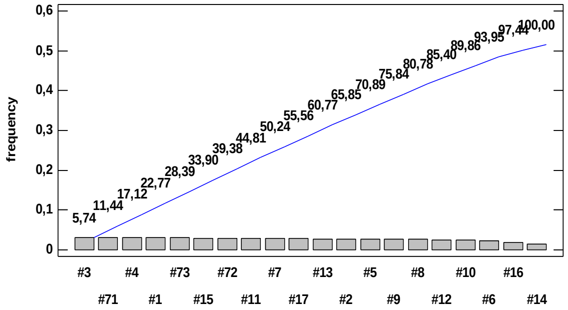
N- Control chart for Hardness (N).



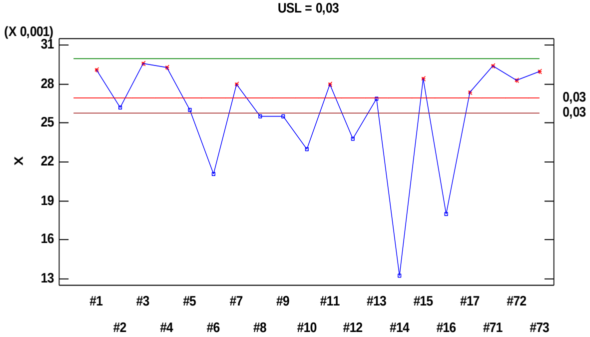
O- Process Capability/Performance Indices for Hardness (N).



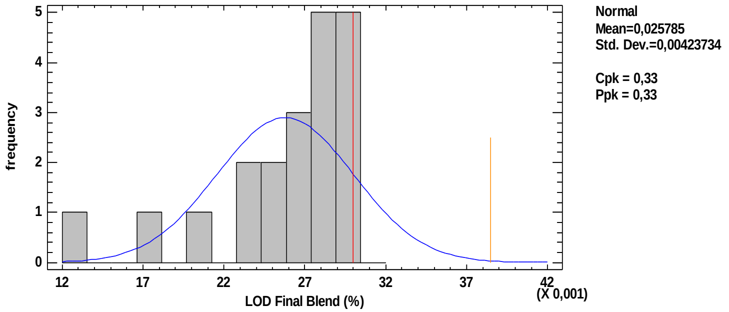
P- Pareto chart for Final Blend LOD (%).



Q- Control chart for Final Blend LOD (%).



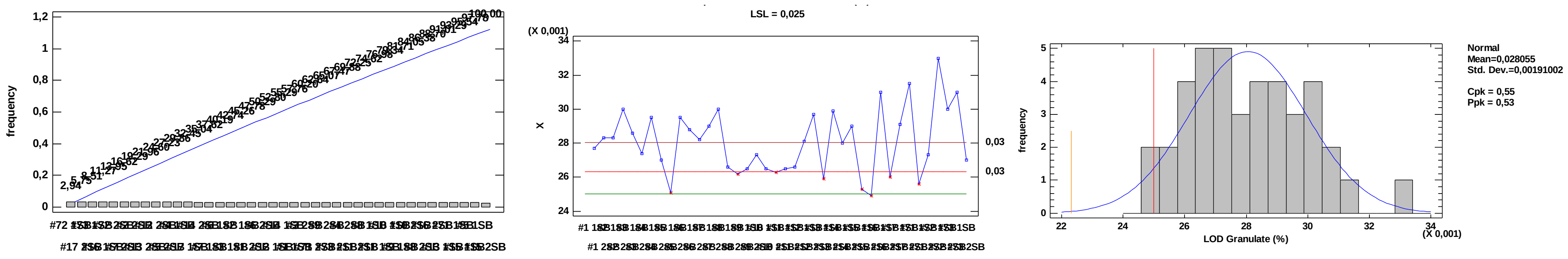
R- Process Capability/Performance Indices for Final Blend LOD (%).



S- Pareto chart for Granulate LOD (%).

T- Control chart for Granulate LOD (%).

U- Process Capability/Performance Indices for Granulate LOD (%).



V- Pareto chart for Thickness (mm).

W- Control chart for Thickness (mm).

X- Process Capability/Performance Indices for Thickness (mm).

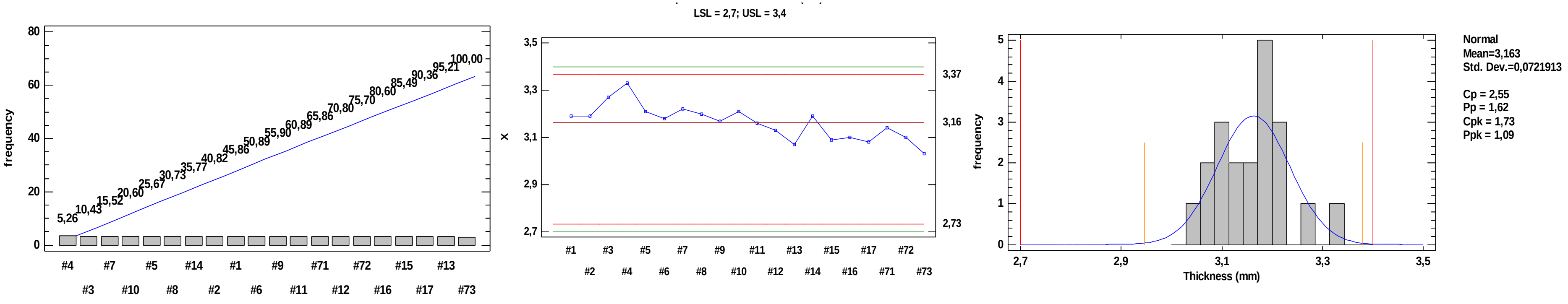
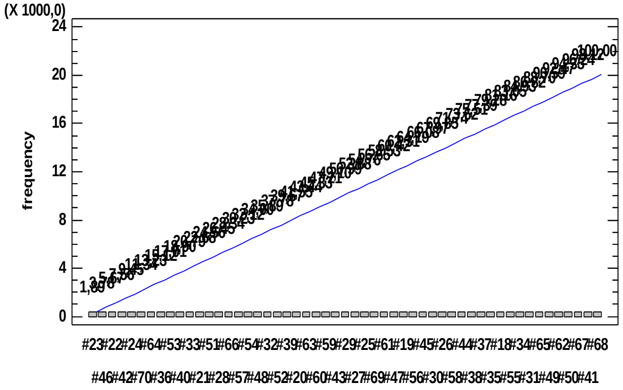


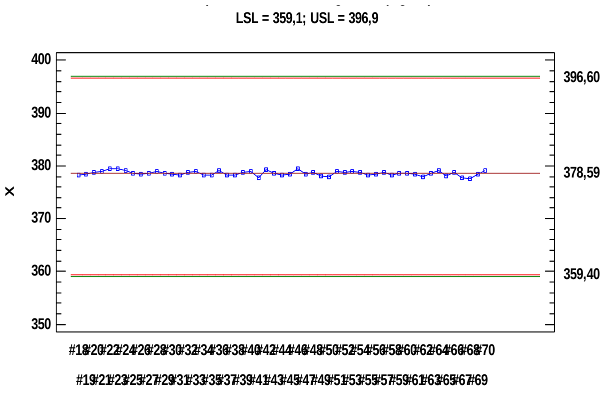
Figure 12- IPC parameters graphics for dosage 1.

- **IPC parameters** graphics for **dosage 2**

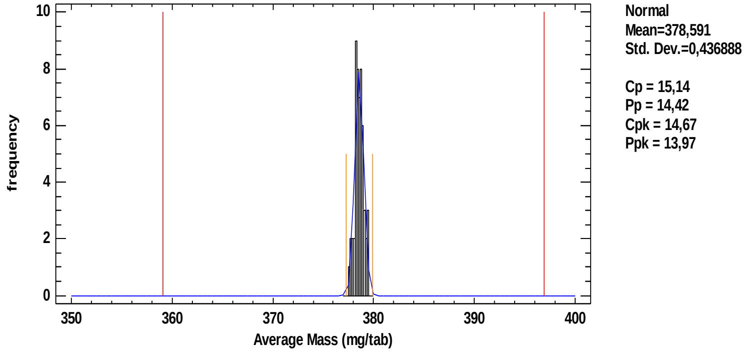
Y- Pareto chart for Average Mass (mg/tab).



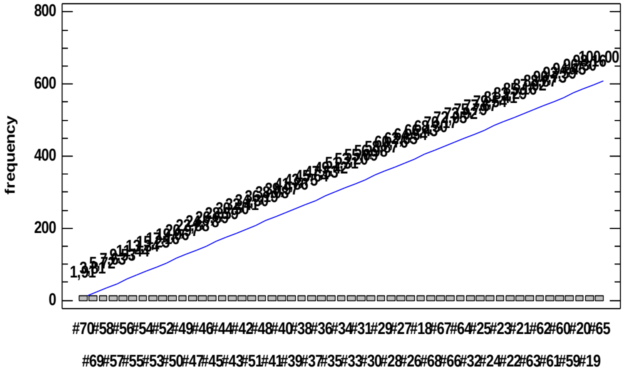
Z- Control chart for Average Mass (mg/tab).



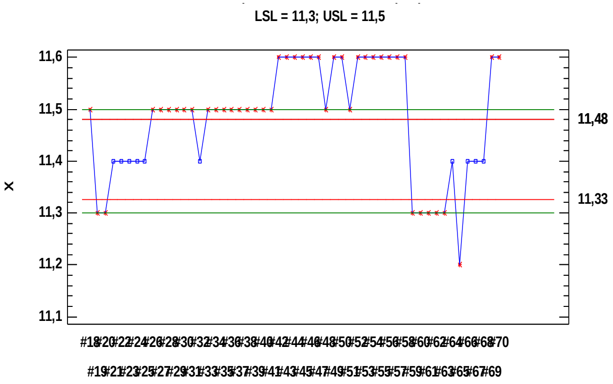
AA- Process Capability/Performance Indices for Average Mass (mg/tab).



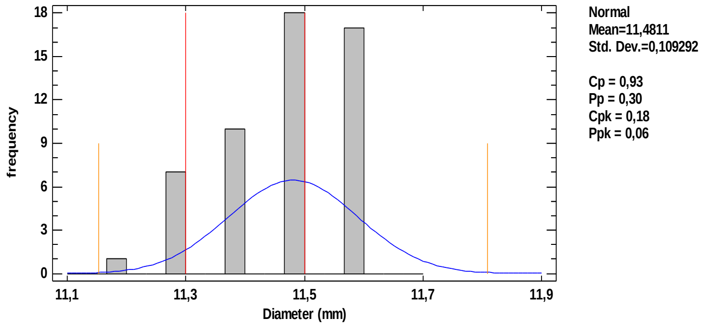
BB- Pareto chart for Diameter (mm).



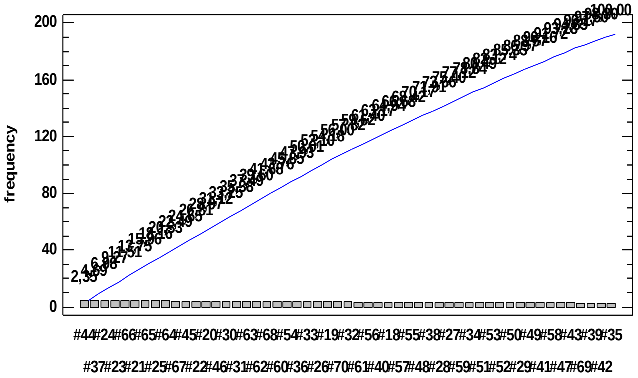
CC- Control chart for Diameter (mm).



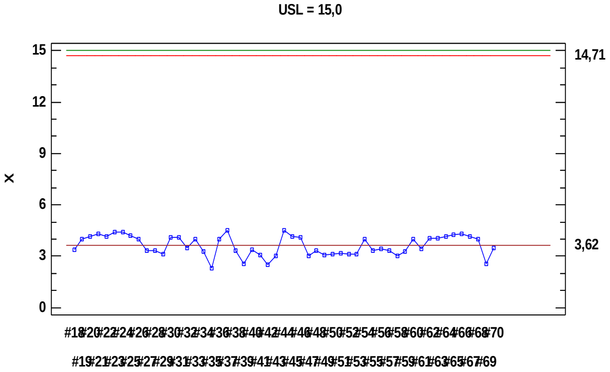
DD- Process Capability/Performance Indices for Diameter (mm).



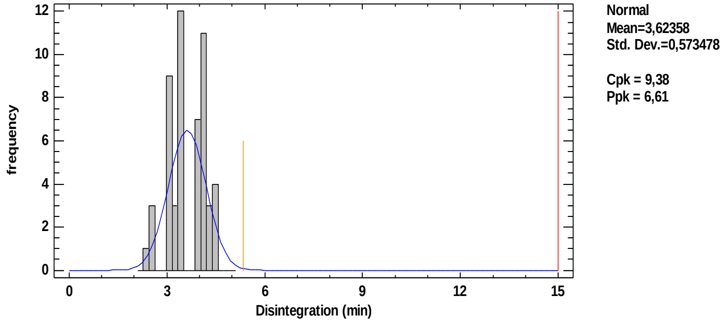
EE- Pareto chart for Disintegration (min).



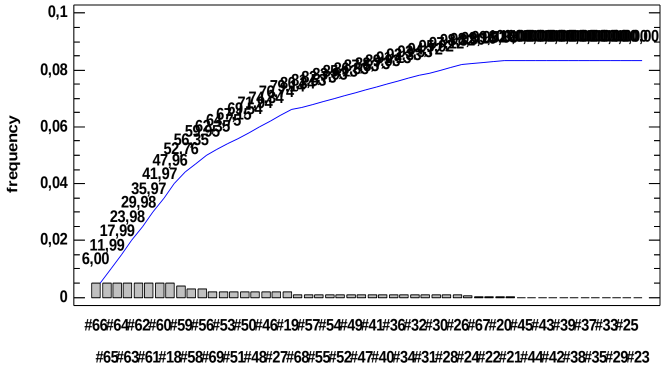
FF- Control chart for Disintegration (min).



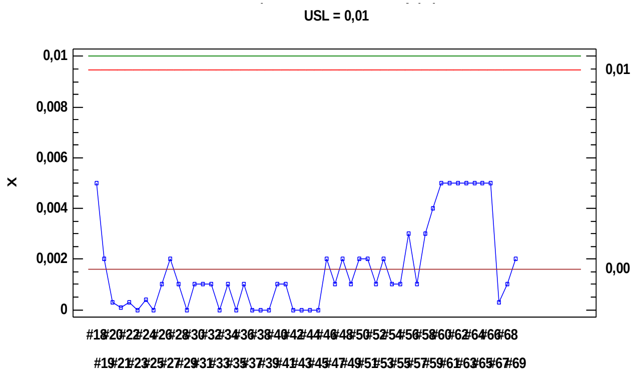
GG- Process Capability/Performance Indices for Disintegration (min).



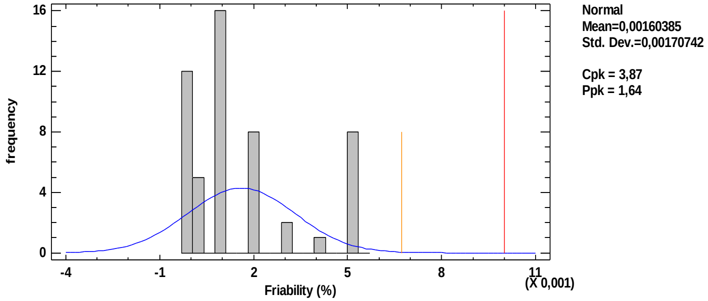
HH- Pareto chart for Friability (%).



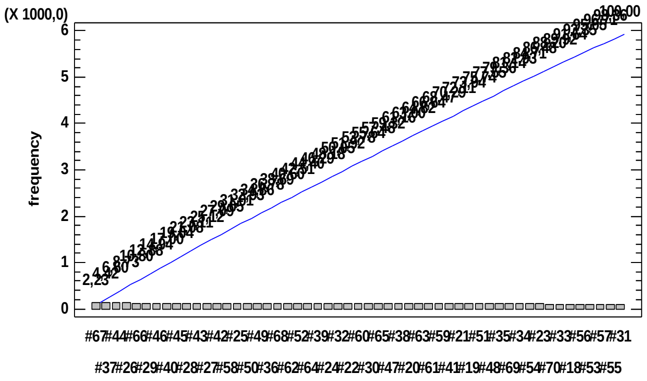
II- Control chart for Friability (%).



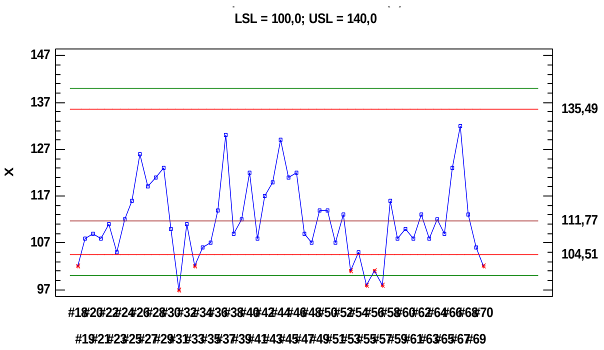
JJ- Process Capability/Performance Indices for Friability (%).



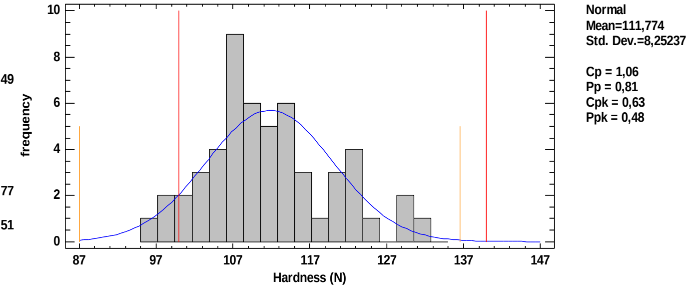
KK- Pareto chart for <u>Hardness</u> (N).



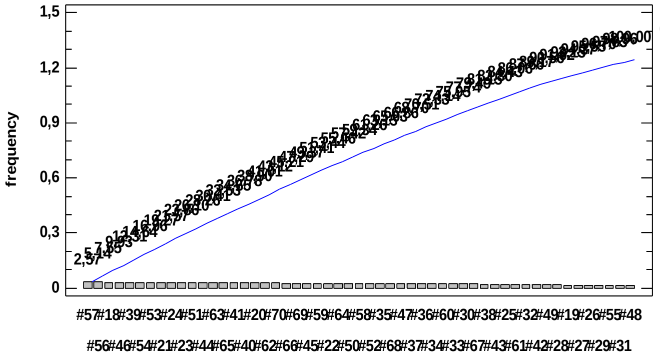
LL- Control chart for <u>Hardness</u> (N).



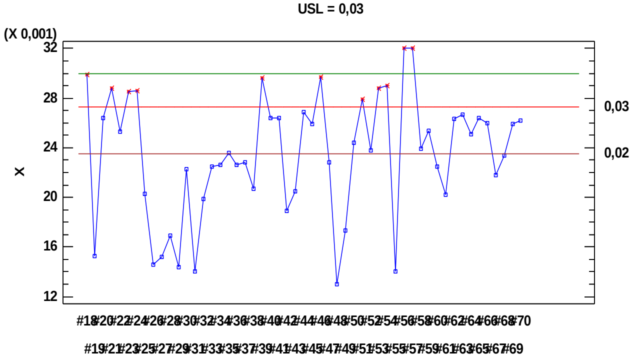
MM- Process Capability/Performance Indices for <u>Hardness</u> (N).



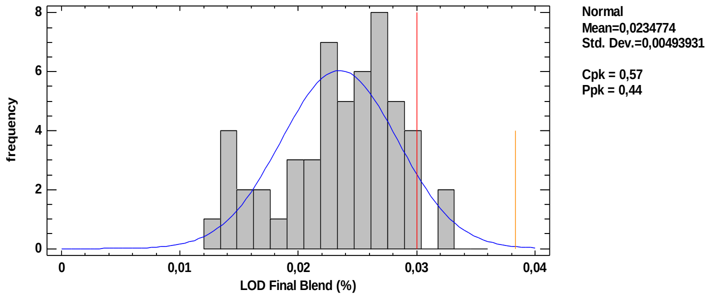
NN- Pareto chart for Final Blend LOD (%).

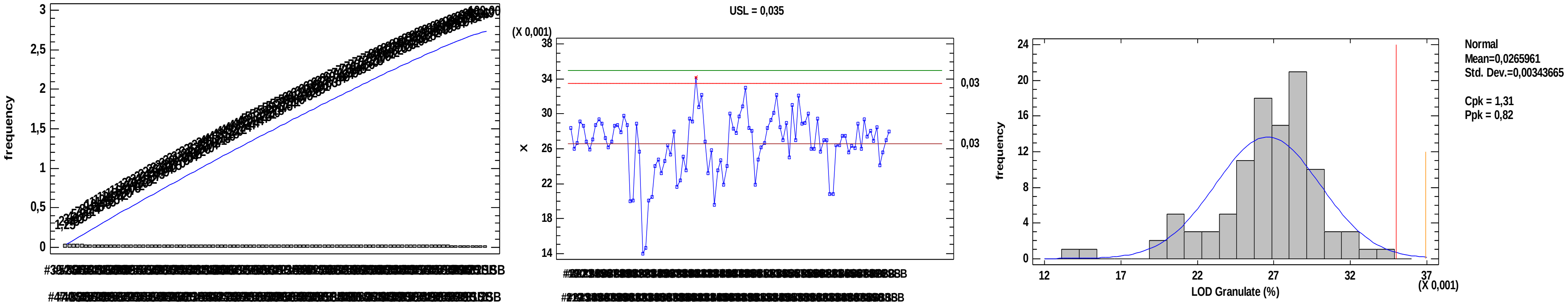


OO- Control chart for Final Blend LOD (%).



PP- Process Capability/Performance Indices for <u>Final Blend LOD</u> (%).

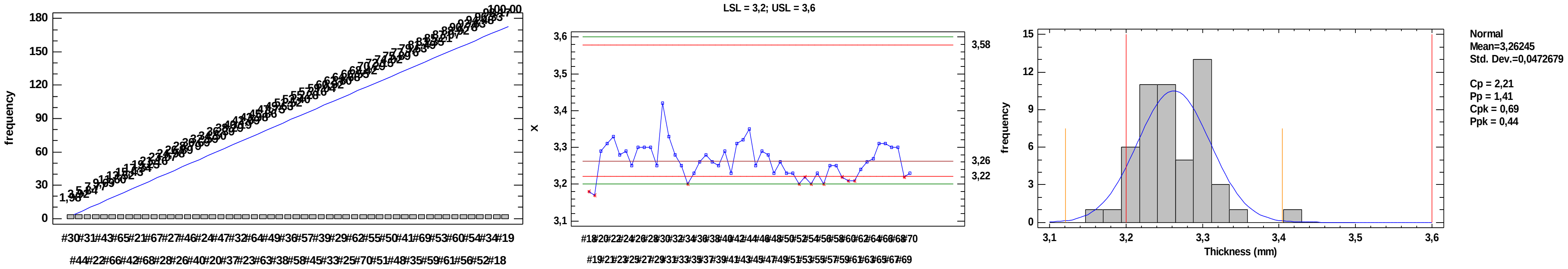




QQ- Pareto chart for Granulate LOD (%).

RR- Control chart for Granulate LOD (%).

SS- Process Capability/Performance Indices for Granulate LOD (%).



TT- Pareto chart for Thickness (mm).

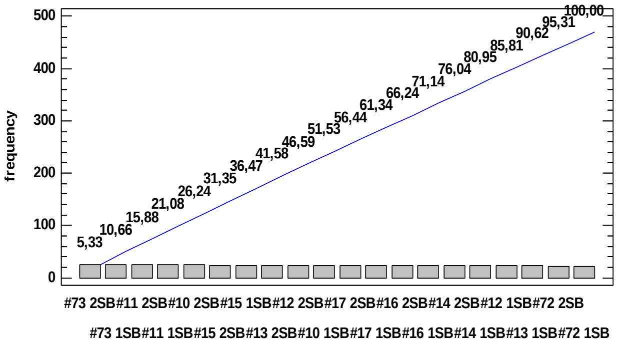
UU- Control chart for Thickness (mm).

VV- Process Capability/Performance Indices for Thickness (mm).

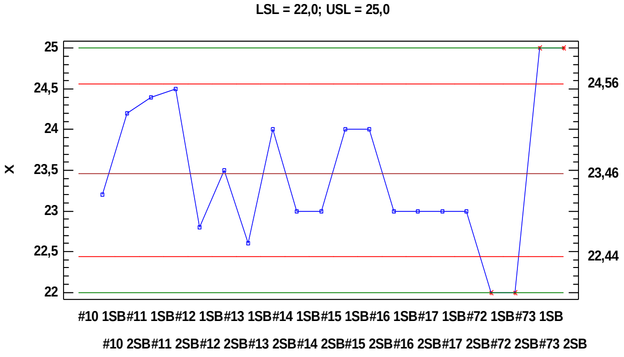
Figure 13- IPC parameters graphics for dosage 2.

- Equipment parameters graphics for **Granulation** for **dosage 1**

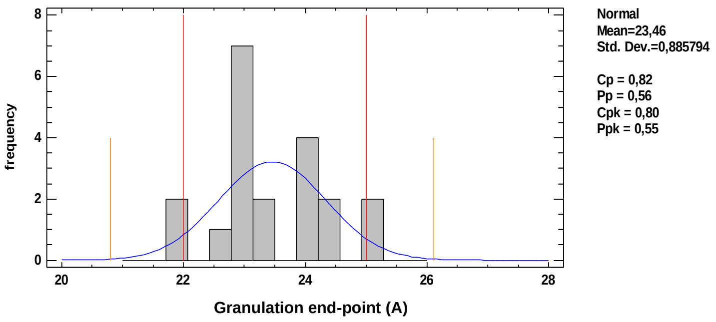
WW- Pareto chart for Granulation end-point (A), Equipment B.



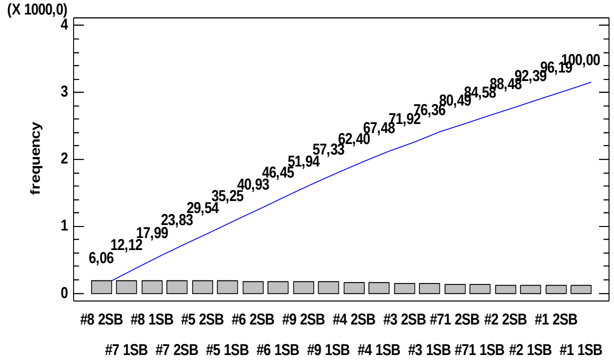
XX- Control chart for Granulation end-point (A), Equipment B.



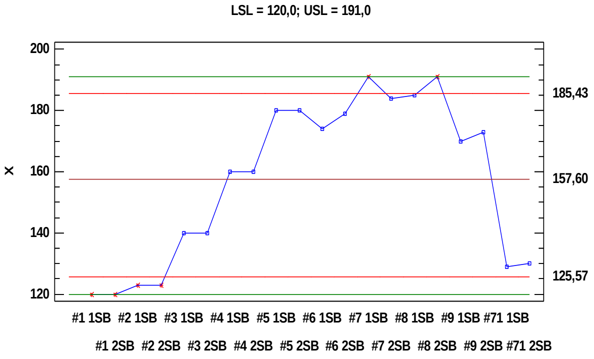
YY- Process Capability/Performance Indices for Granulation end-point (A), Equipment B.



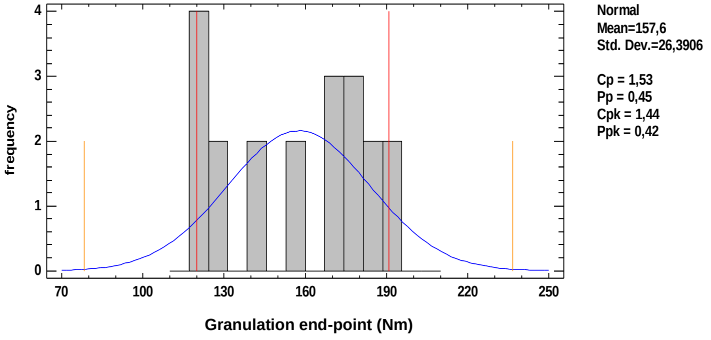
ZZ- Pareto chart for Granulation end-point (Nm), Equipment A.



AAA- Control chart for Granulation end-point (Nm), Equipment A.



BBB- Process Capability/Performance Indices for Granulation end-point (Nm), Equipment A.



CCC- Pareto chart for <u>Peristaltic Pump Speed</u> (rpm), Equipment A.

DDD- Control chart for <u>Peristaltic Pump Speed</u> (rpm), Equipment A.

EEE- Process Capability/Performance Indices for <u>Peristaltic Pump Speed</u> (rpm), Equipment A.

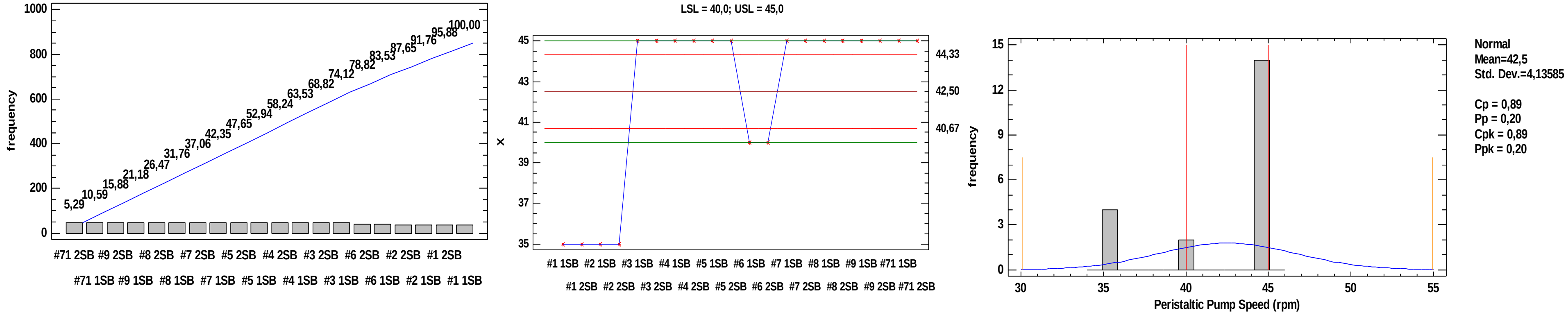
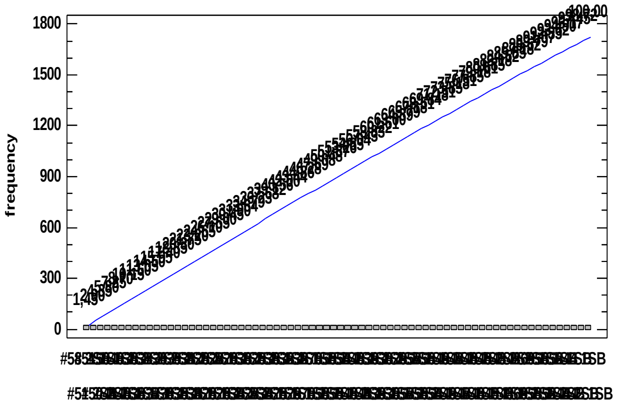


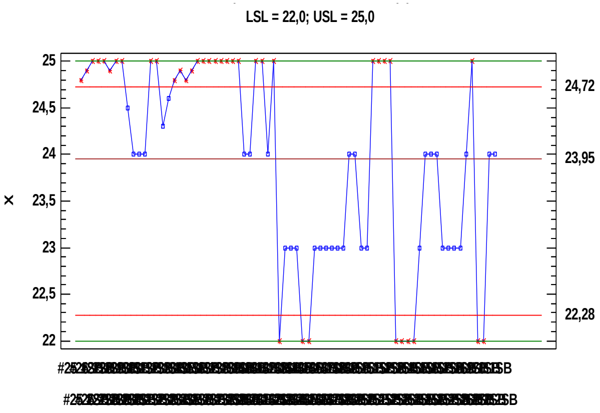
Figure 14- Equipment parameters graphics for Granulation for dosage 1.

- <u>Equipment parameters graphics for **Granulation** for **dosage 2**</u>

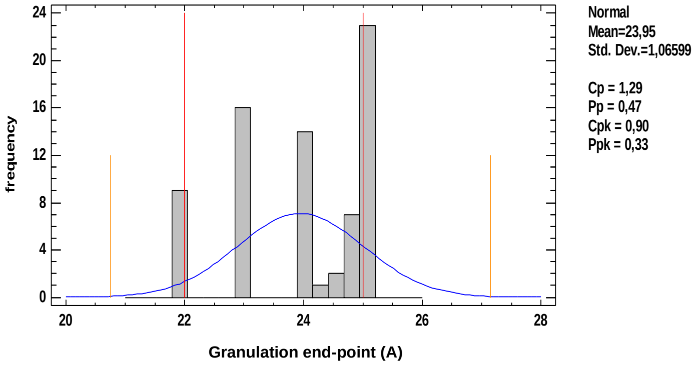
FFF- Pareto chart for <u>Granulation end-point</u> (A), Equipment B.

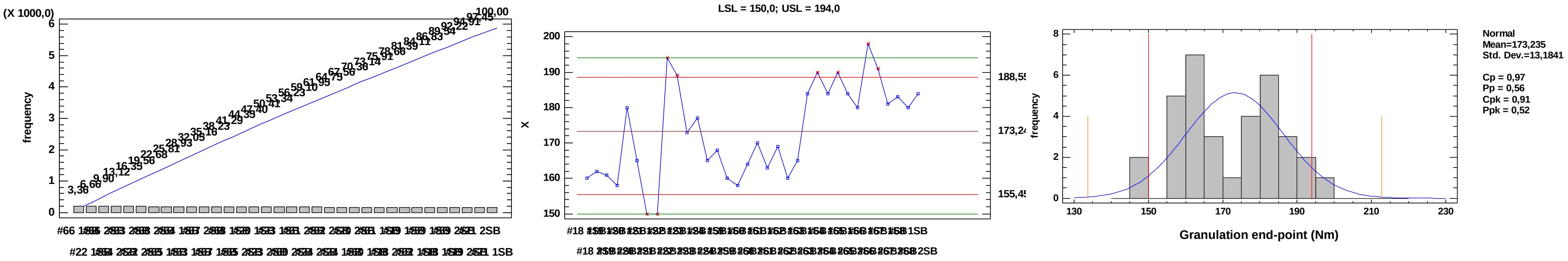


GGG- Control chart for <u>Granulation end-point</u> (A), Equipment B.



HHH- Process Capability/Performance Indices for <u>Granulation end-point</u> (A), Equipment B.

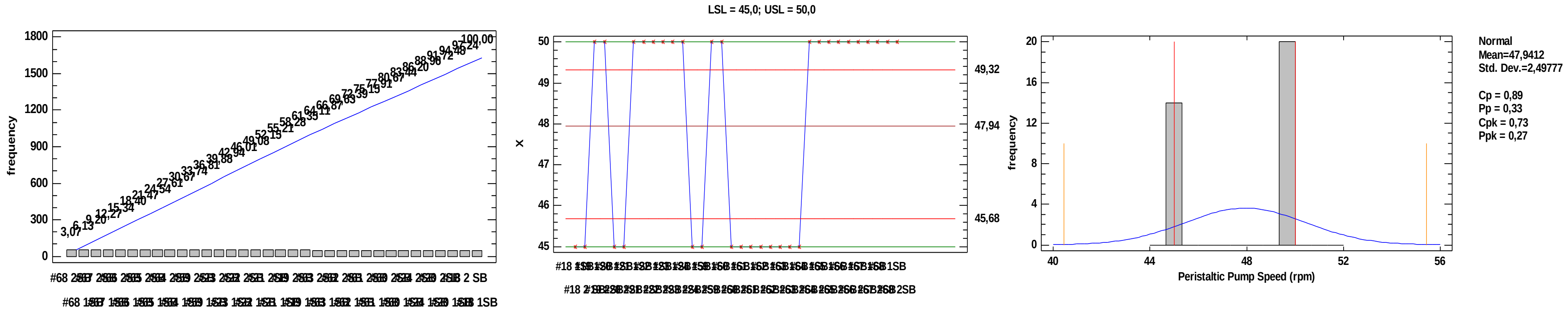




III- Pareto chart for Granulation end-point (Nm), Equipment A.

JJJ- Control chart for Granulation end-point (Nm), Equipment A.

KKK- Process Capability/Performance Indices for Granulation end-point (Nm), Equipment A.



LLL- Pareto chart for Peristaltic Pump Speed (rpm), Equipment A.

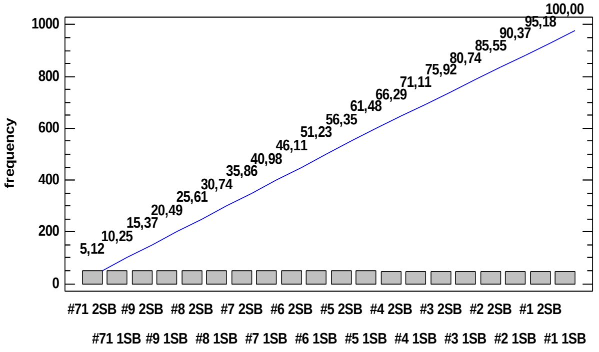
MMM- Control chart for Peristaltic Pump Speed (rpm), Equipment A.

NNN- Process Capability/Performance Indices for Peristaltic Pump Speed (rpm), Equipment A.

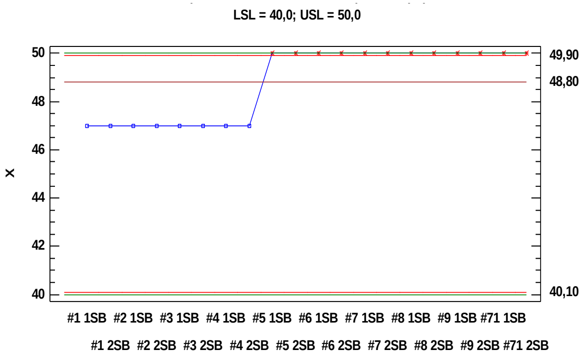
Figure 15- Equipment parameters graphics for Granulation for dosage 2.

- Equipment parameters graphics for **Drying** for **dosage 1**

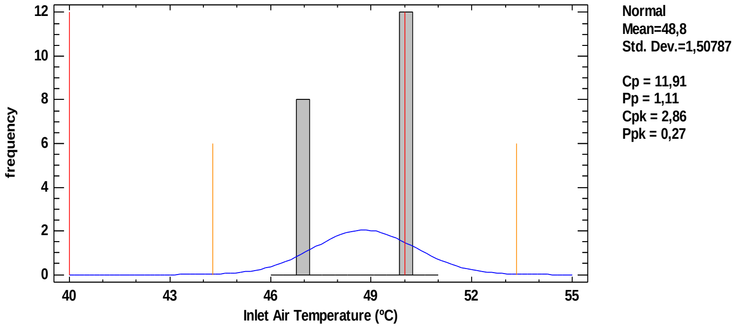
OOO- Pareto chart for Inlet Air Temperature (ºC), Equipment C.



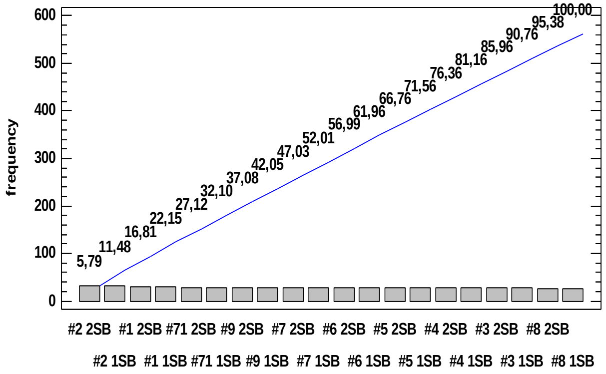
PPP- Control chart for Inlet Air Temperature (ºC), Equipment C.



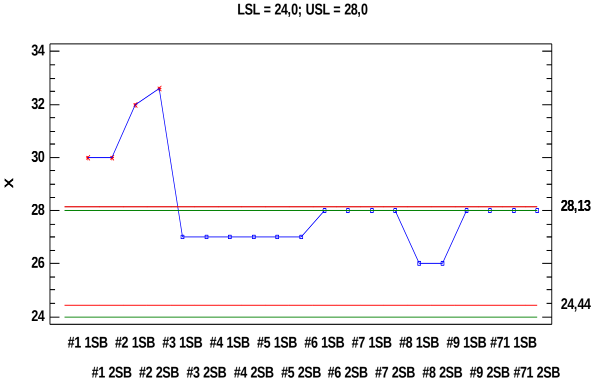
QQQ- Process Capability/Performance Indices for Inlet Air Temperature (ºC), Equipment C.



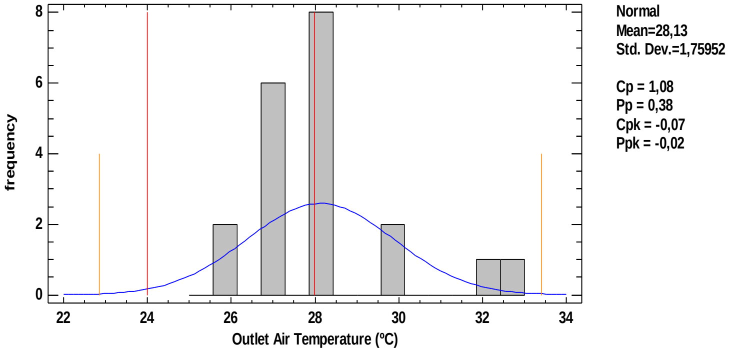
RRR- Pareto chart for Inlet Air Volume (m^3/h),



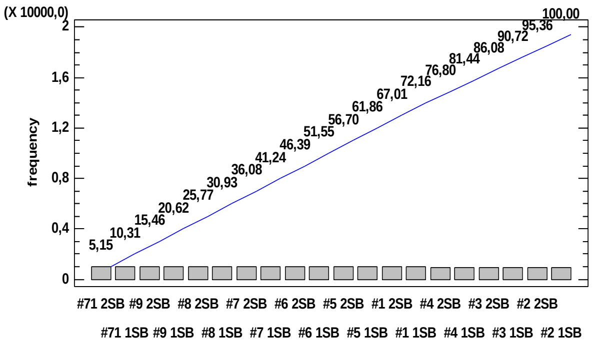
SSS- Control chart for Inlet Air Volume (m^3/h),



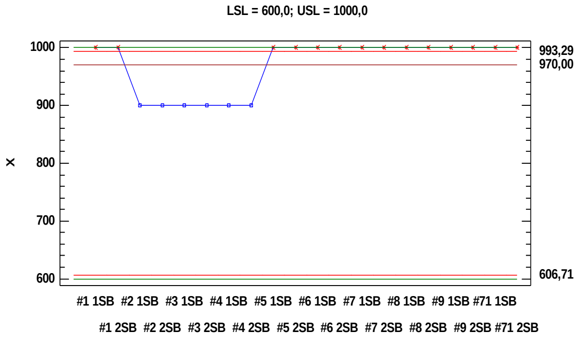
TTT- Process Capability/Performance Indices for Inlet Air Volume (m^3/h), Equipment C.



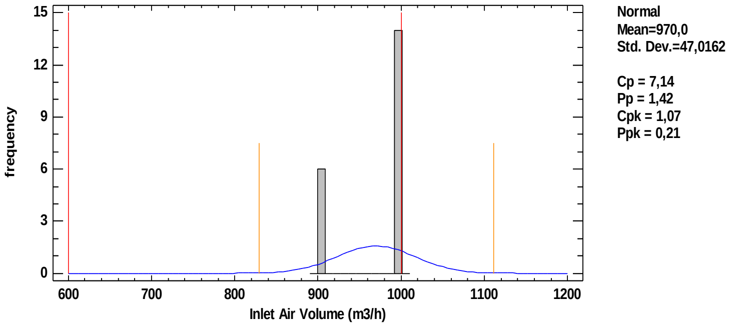
UUU- Pareto chart for Outlet Air Temperature (ºC), Equipment C.



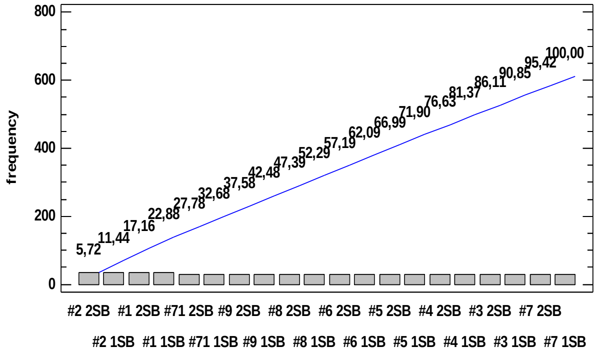
VVV- Control chart for Outlet Air Temperature (ºC), Equipment C.



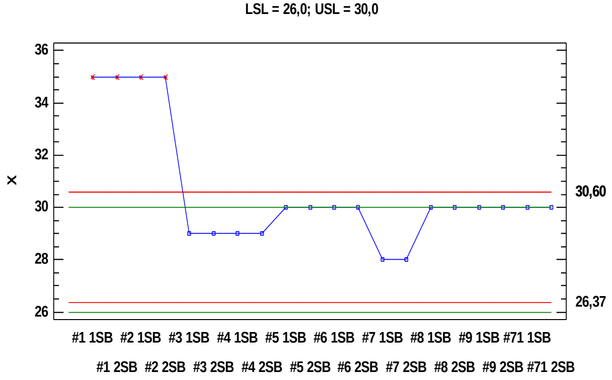
WWW- Process Capability/Performance Indices for Outlet Air Temperature (ºC), Equipment C.



XXX- Pareto chart for Product Temperature (ºC), Equipment C.



YYY- Control chart for Product Temperature (ºC), Equipment C.



ZZZ- Process Capability/Performance Indices for Product Temperature (ºC), Equipment C.

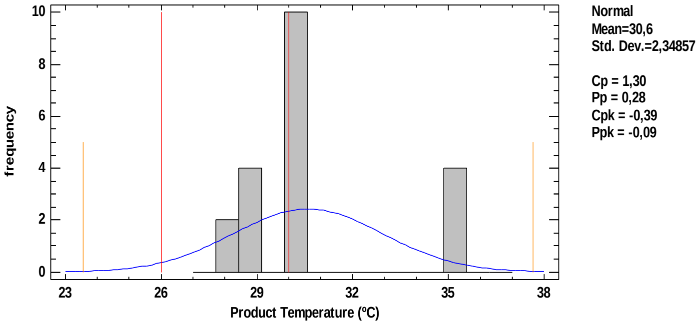
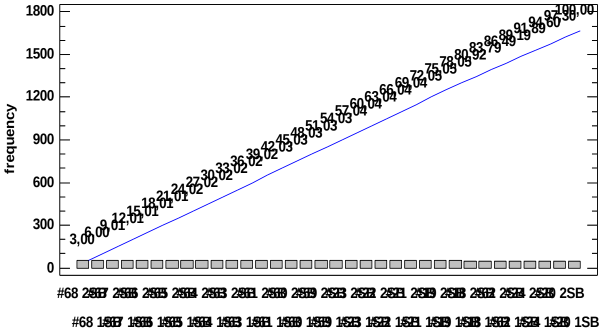


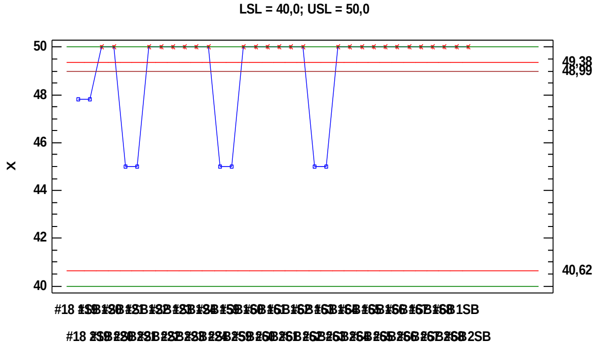
Figure 16- Equipment parameters graphics for Drying for dosage 1.

- Equipment parameters graphics for **Drying** for **dosage 2**

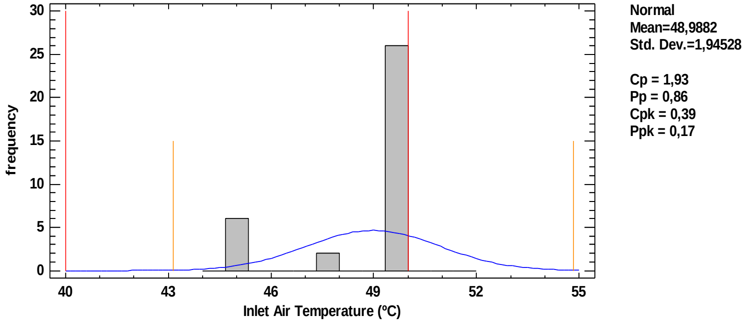
AAAA- Pareto chart for Inlet Air Temperature (ºC), Equipment C.



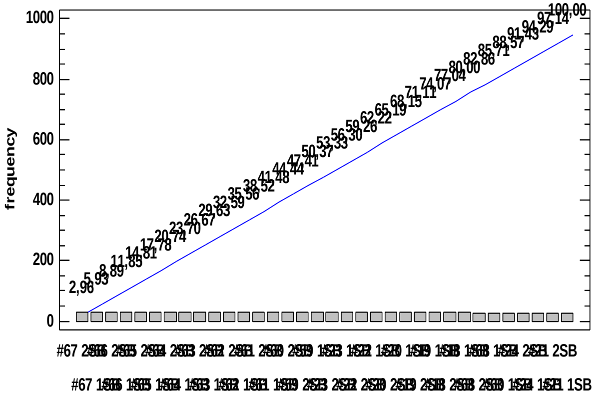
BBBB- Control chart for Inlet Air Temperature (ºC), Equipment C.



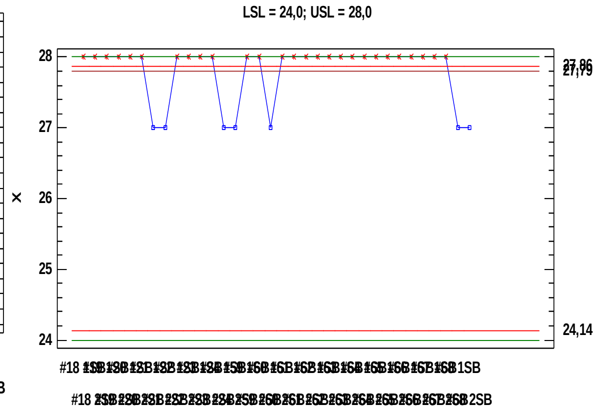
CCCC- Process Capability/Performance Indices for Inlet Air Temperature (ºC), Equipment C.



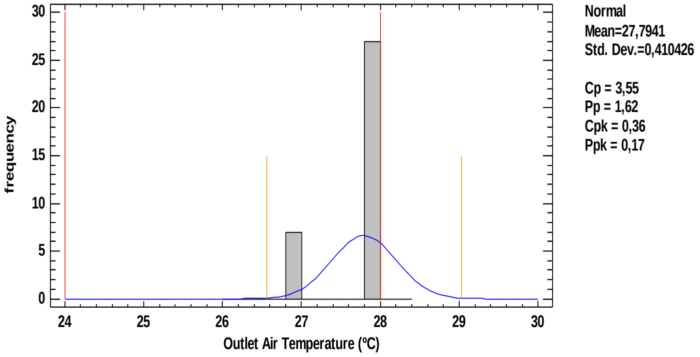
DDDD- Pareto chart for Outlet Air Temperature (ºC), Equipment C.



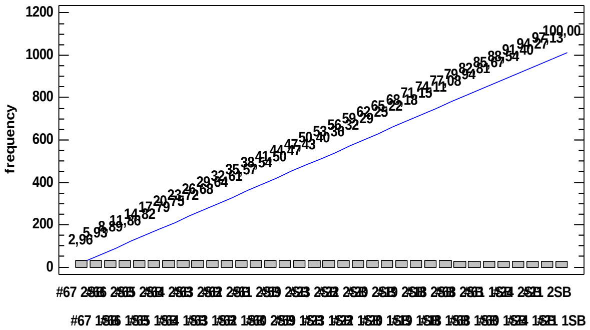
EEEE- Control chart for Outlet Air Temperature (ºC), Equipment C.



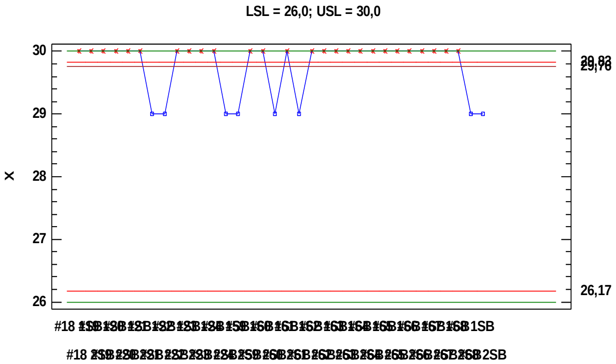
FFFF- Process Capability/Performance Indices for Outlet Air Temperature (ºC), Equipment C.



GGGG- Pareto chart for Product Temperature (ºC), Equipment C.



HHHH- Control chart for Product Temperature (ºC), Equipment C.



IIII- Process Capability/Performance Indices for Product Temperature (ºC), Equipment C.

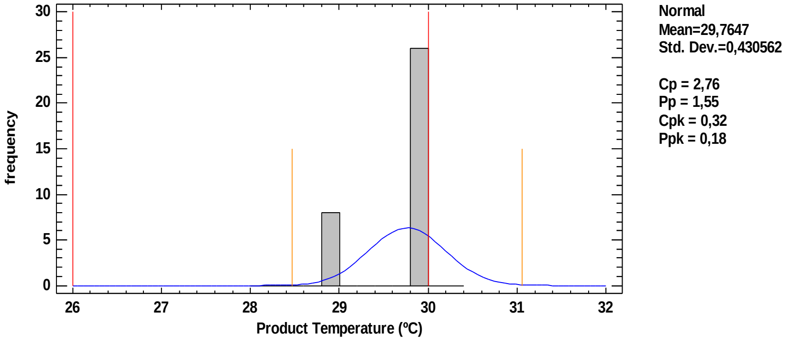
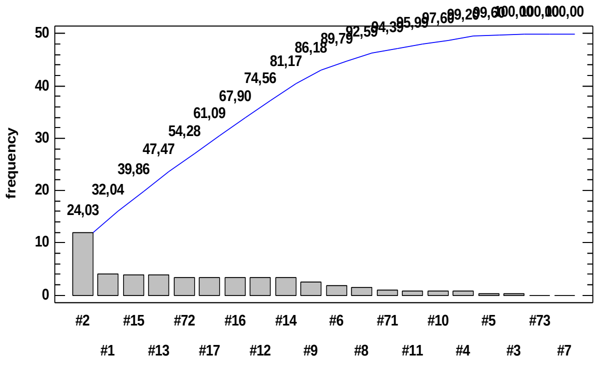


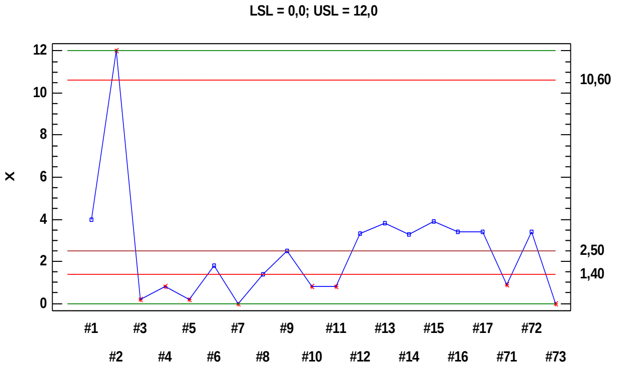
Figure 17- Equipment parameters graphics for Drying for dosage 2.

- <u>Equipment parameters graphics for **Compression** for **dosage 1**</u>

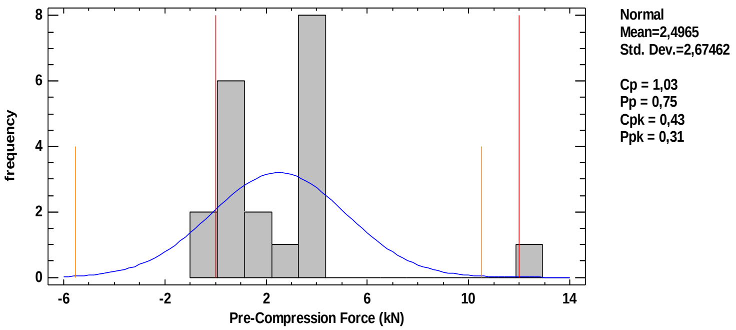
JJJJ- Pareto chart for <u>Pre-Compression Force</u> (kN).



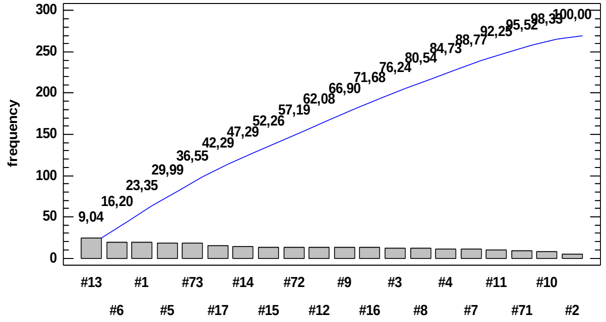
KKKK- Control chart for <u>Pre-Compression Force</u> (kN).



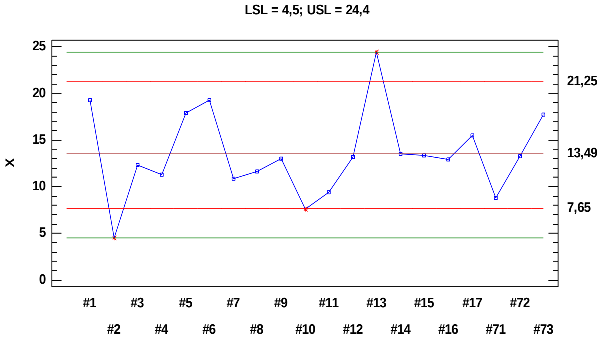
LLLL- Process Capability/Performance Indices for <u>Pre-Compression Force</u> (kN).



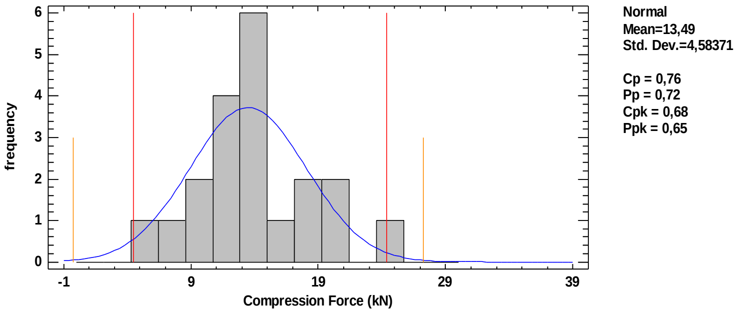
MMMM- Pareto chart for <u>Compression Force</u> (kN).



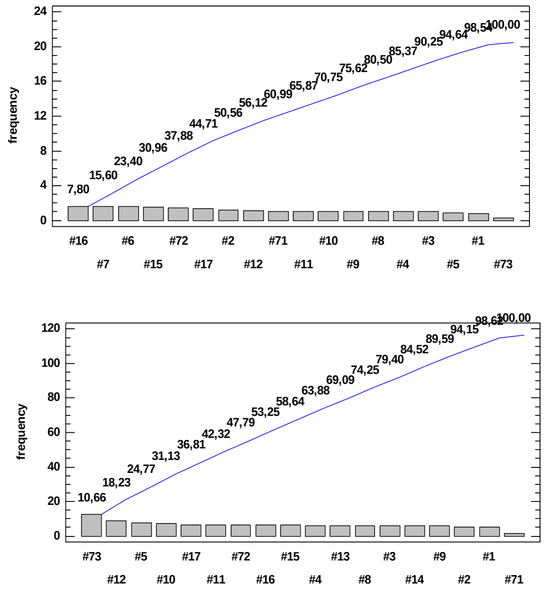
NNNN- Control chart for <u>Compression Force</u> (kN).



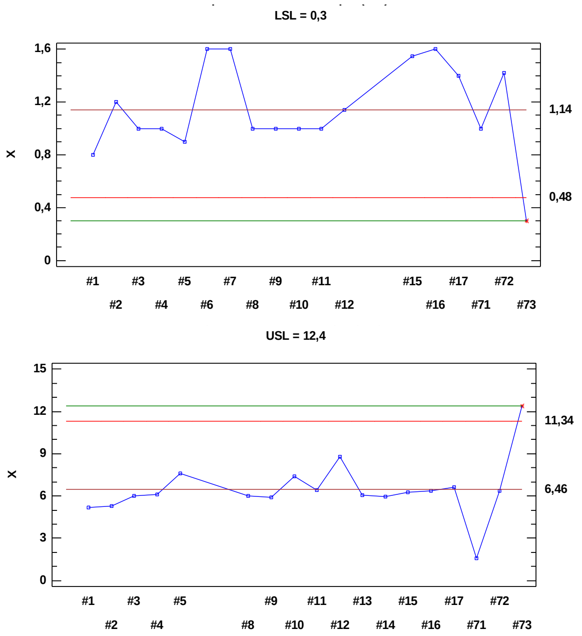
OOOO- Process Capability/Performance Indices for <u>Compression Force</u> (kN).



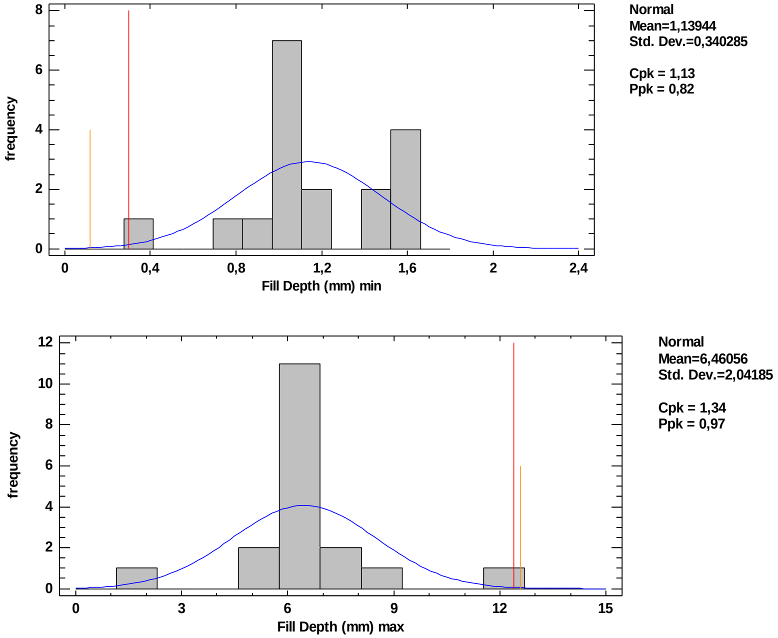
PPPP- Pareto chart for Fill Depth (mm).



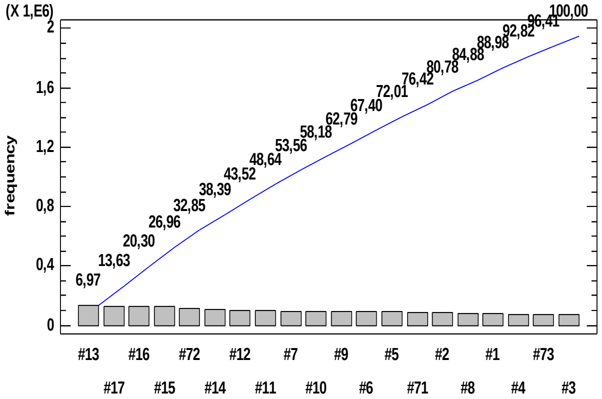
QQQQ- Control chart for Fill Depth (mm).



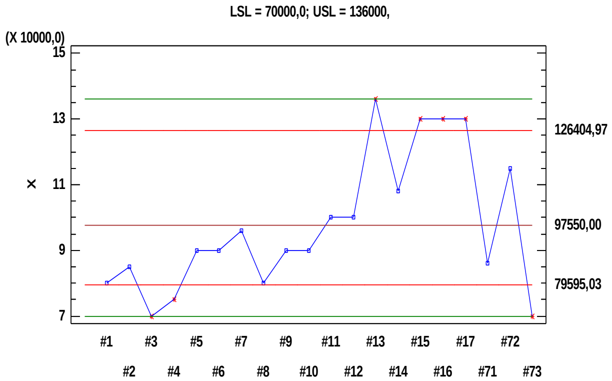
RRRR- Process Capability/Performance Indices for Fill Depth (mm).



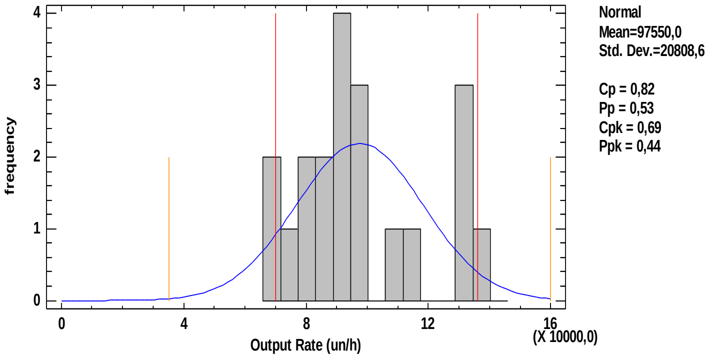
SSSS- Pareto chart for Output Rate (un/h).



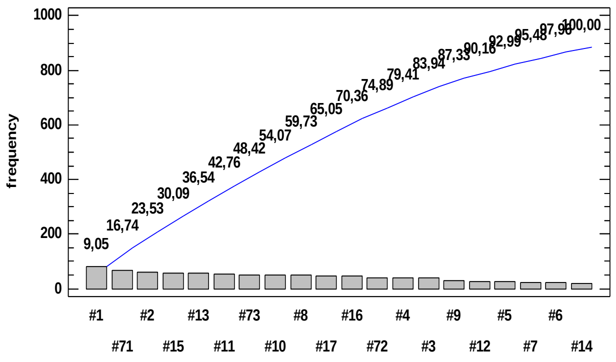
TTTT- Control chart for Output Rate (un/h).



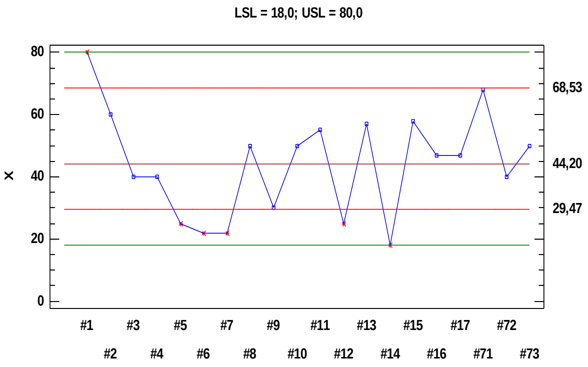
UUUU- Process Capability/Performance Indices for Output Rate (un/h).



VVVV- Pareto chart for Feed Shoe Settings (rpm).



WWWW- Control chart for Feed Shoe Settings (rpm).



XXXX- Process Capability/Performance Indices for Feed Shoe Settings (rpm).

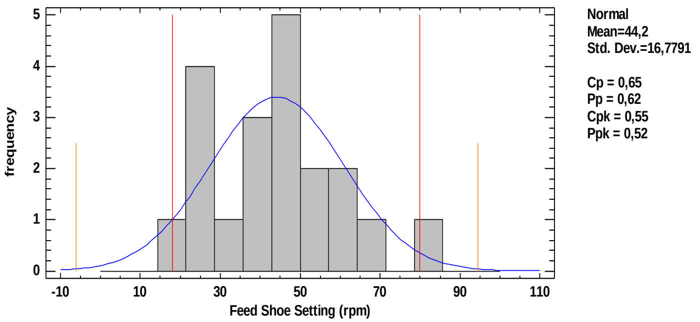
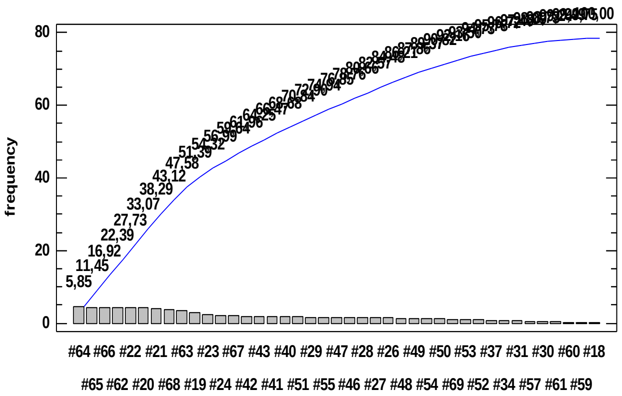


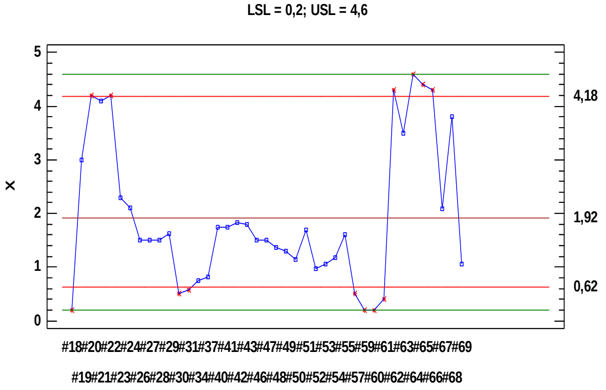
Figure 18- Equipment parameters graphics for Compression for dosage 1.

- Equipment parameters graphics for **Compression** for **dosage 2**

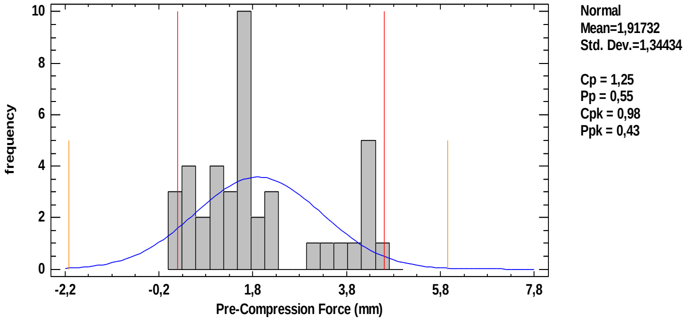
YYYY- Pareto chart for Pre-Compression Force (mm).



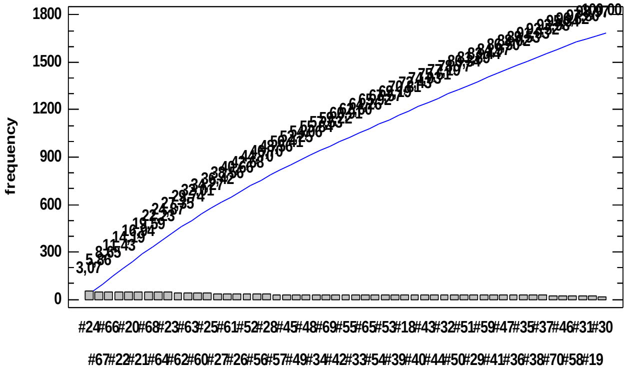
ZZZZ- Control chart for Pre-Compression Force (mm).



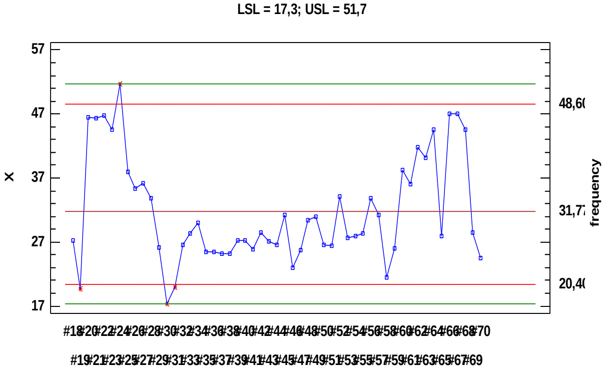
AAAAA- Process Capability/Performance Indices for Pre-Compression Force (mm).



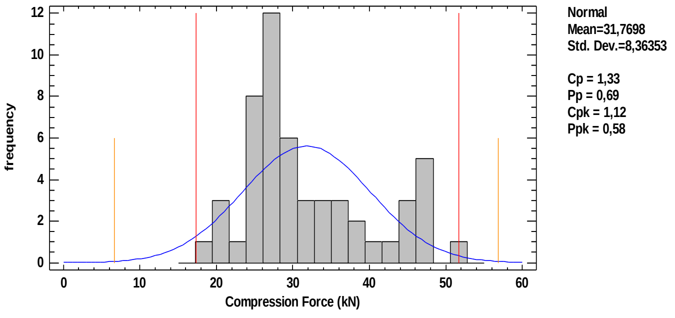
BBBBB- Pareto chart for Compression Force (kN).



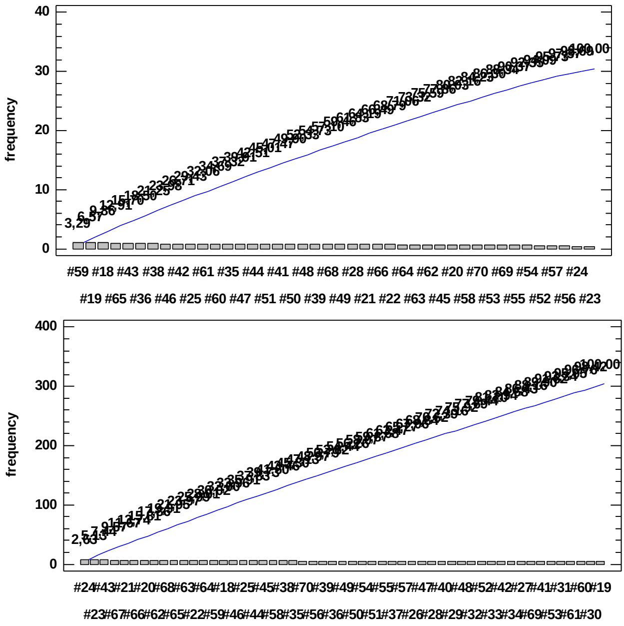
CCCCC- Control chart for Compression Force (kN).



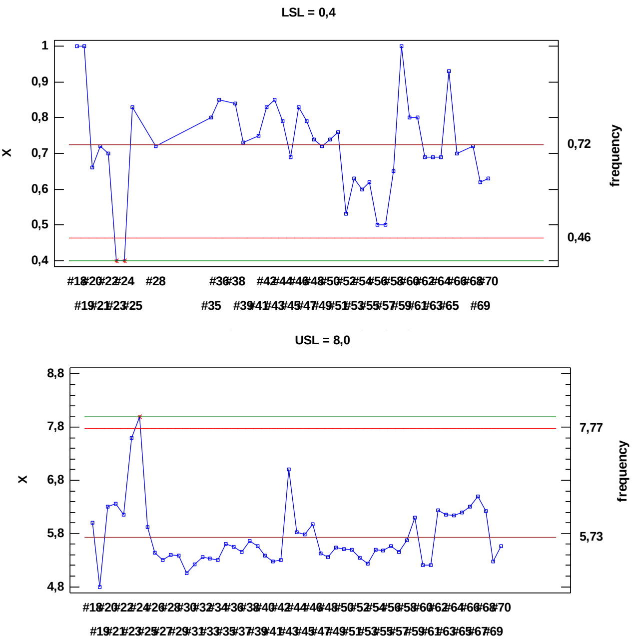
DDDDD- Process Capability/Performance Indices for Compression Force (kN).



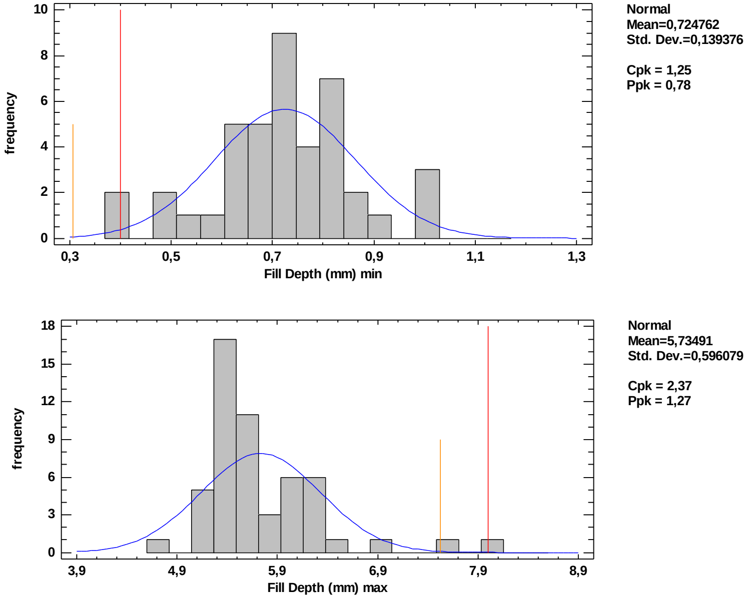
EEEEE- Pareto chart for Fill Depth (mm).



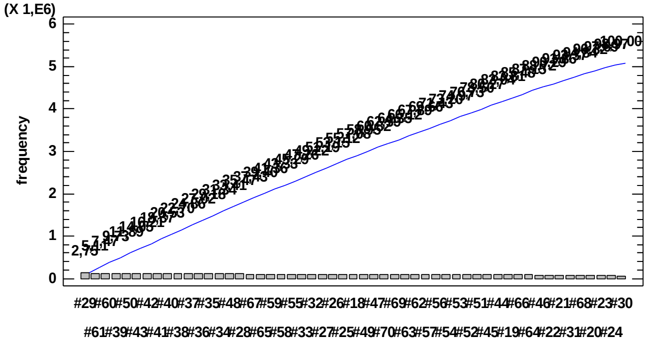
FFFFF- Control chart for Fill Depth (mm).



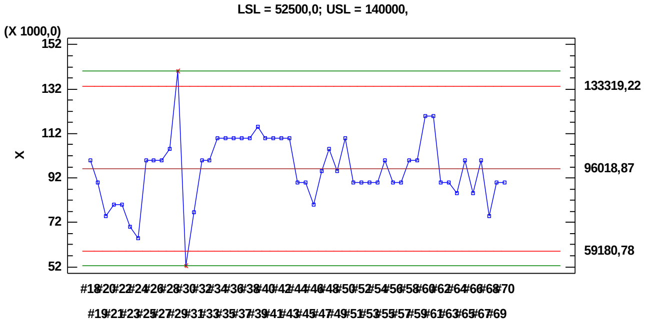
GGGGG- Process Capability/Performance Indices for Fill Depth (mm).



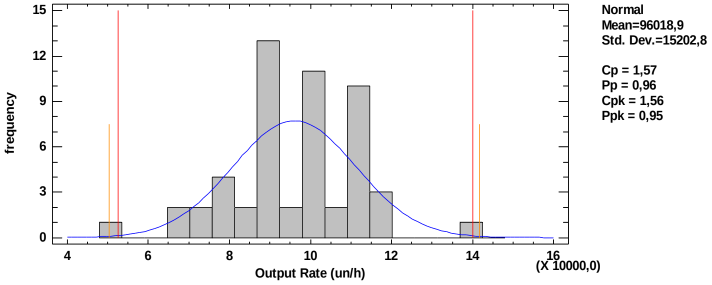
EEEEE- Pareto chart for Output Rate (un/h).



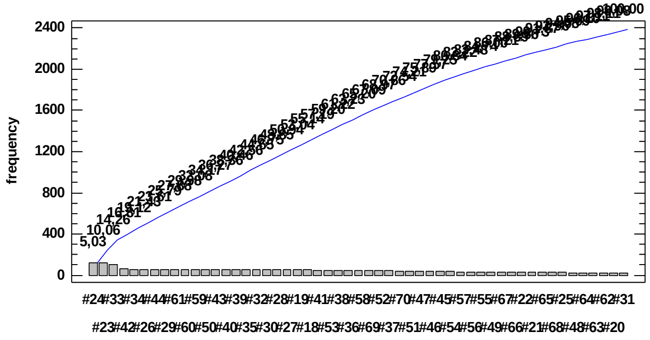
FFFFF- Control chart for Output Rate (un/h).



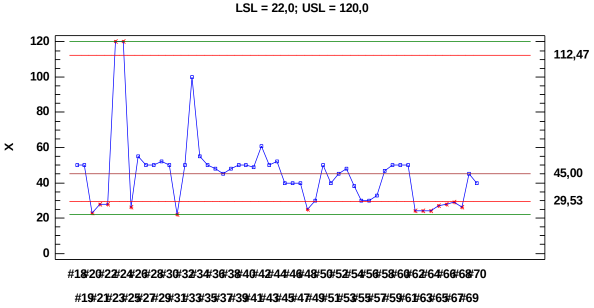
GGGGG- Process Capability/Performance Indices for Output Rate (un/h).



EEEEE- Pareto chart for Feed Shoe Settings (rpm).



FFFFF- Control chart for Feed Shoe Settings (rpm).



GGGGG- Process Capability/Performance Indices for Feed Shoe Settings (rpm).

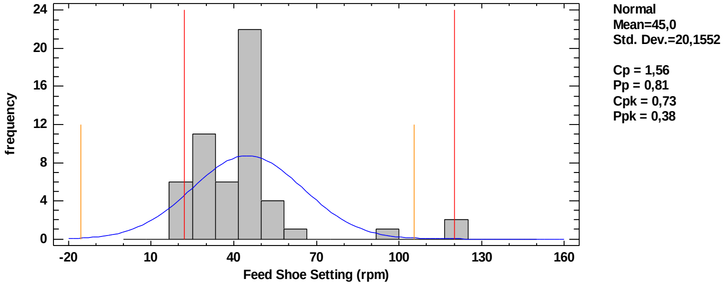


Figure 19- Equipment parameters graphics for Compression for dosage 2.