Universidade de Lisboa

Faculdade de Farmácia

Evaluation of the cost-benefit of the implementation of PAT systems for the production of solid forms in a pharmaceutical company

Pedro Miguel António Cordeiro

Master Course in Pharmaceutical Engineering

Master Thesis

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Abstract

Process Analytical Technology (PAT) is defined by the FDA in the PAT initiative issued in 2004 as ”a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and inprocess materials and processes, with the goal of ensuring the final product quality”. Since then, the pharmaceutical companies have been adopting gradually this technology in their manufacturing lines. PAT tools are indeed well recognized as a critical tool for achieving better process and product control leading to the possibility of real time release testing. This thesis evaluated the technical and economic feasibility of implementation of PAT systems into a Portuguese pharmaceutical company manufacturing line of solid forms. To accomplish this task, two products were used as models. These products were selected since they cover most unit operations of the solid forms installed manufacturing line. The work was divided in two parts. The first part is concerned with the identification of critical quality attributes (CQAs) and critical process parameters (CPPs) of the two model products in order for the proposition of opportunities of implementation of PAT strategies. These opportunities are described in detail and evaluated according to a series of criteria. Nine opportunities were identified, mainly involving NIR and RAMAN spectroscopy as suitable technology. The implementation of the identified opportunities, is expected to permit the possibility of real time release for the two products. The second part focuses on the economical feasibility of the identified PAT implementation. The economic analysis indicated that the implementation of all opportunities will reduce manufacturing/quality control time and costs substantially. The expectation of return-of-investment is achieved in a time frame between 5 to 8 years respectively considering optimistic and pessimist scenarios.

Keywords: Process Analytical Technology; Near Infrared; Quality-by-design; Economic analysis; Real time release

Resumo

Tecnologia Analítica de Processo (PAT) é definida pela FDA em 2004 como ”o sistema para desenhar, analisar e controlar o processo por mediões constantes (por exemplo, durante o processo) dos parâmetros críticos e de qualidade da matria - prima, produtos intermédios e do processo, com o objetivo de assegurar a qualidade do produto final”. Desde esse momento, as empresas farmacêuticas têm vindo a adotar gradualmente este tipo de tecnologia nas suas linhas de produção. As ferramentas PAT têm vindo a ser gradualmente adotadas como ferramentas chave para um melhor controlo do processo e do produto levando à possibilidade de real time release testing. Esta tese avaliou a viabilidade técnica e económica da implementação de um sistema PAT em uma linha de produção de formas farmacâuticas sélidas de uma empresa portuguesa. Para se poder realizar esta tarefa, dois produtos foram usados como modelos. Este productos foram escolhidos porque cobrem quase todas as operaes unitárias da linha de produo de formas sólidas. O trabalho está divido em duas partes. A primeira parte tem como objetivo a identificação dos parâmetros críticos de qualidade (CQAs) e dos parmetros críticos do processo (CPPs) dos dois produtos de referência de modo a propor oportunidades de implementao de estratégias PAT. Estas oportunidades são descritas em detalhe e avaliadas segundo uma série de critérios. Nove oportunidades foram identificadas, nas quais evolvem principalmente espectroscopia NIR e RAMAN como os equipamentos adequados. A implementação destas oportunidades permitiram a possibilidade de real time release para os productos em estudo. A segunda parte est focada na viabilidade económica das oportunidades PAT identificadas. A anlise económica que a implementação de todas as oportunidades vão reduzir substancialmente os custos e tempo do processo de fabrico e controlo de qualidade. É estimado um retorno do investimento entre 5 a 8 anos considerando o cenários otimista e pessimista, respetivamente.

Palavras-chave: Tecnologia Analítica de Processo; Infravermelho próximo; Quality-by-design; Análise Económica; Libertação em tempo real

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Objectives and Motivations

This Thesis serves the objective of analyzing the technical and economic viability of implementation of Process Analytical Technology Systems to assist the manufacturing process of pharmaceuticals in a typical medium-size secondary production pharmaceutical plant. The pharmaceutical production line of Medinfar was selected as a case-study. Additionally two Medinfar pharmaceutical products currently manufactured by the company were considered to investigate the potential benefits and applicability of PAT tools. The thesis aims not only at the identification of critical equipment for the implementation of PAT systems, but also to select the most appropriate PAT solutions for the critical operation units, selection of the most adequate PAT systems. The economic benefit of the implementation of such systems was also investigated based on the two prototype products, through the extrapolation of the potential impact of the technology to the whole company and product pipeline. This thesis should serve as another support tool to assist in the decision of implementing this technology by ranking the implementation opportunities according to their expected scientific impact, productivity impact, knowledge gain impact and revenue.

With this analysis, we intend to identify implementation opportunities for PAT systems in the manufacturing line used by these two products. This study will be focused on the identification of critical quality attributes (CQAs) and critical process parameters (CPPs) of X and Y products manufacturing. The thesis is divided essentially in two sections: the technical implementation and economic viability.

With the implementation of PAT systems, one aims at a continuous process improvement and knowledge, through a more efficient control of CQAs. The introduction of this technology is not solely important for quality assurance/control, but also for development department potentially shortening time when a new product development is required.

Abbreviations

API: Active Pharmaceutical Ingredient

CU: Content Uniformity

EMA/EMEA: European Medicines Agency

EBIT: Earning Before Interest and Taxes

FDA: Food and Drug Administration

FT: Fourier-transform

HPLC: High Pressure Liquid Chromatographie

ICH: International Conference on Harmonization

IPC: In Process Control

IRR: Internal Rate of Return

LOD: Loss on Drying

NIR: Near Infrared

NPV: Net Present Value

OFAT: One-Factor-at-a-Time

PAT: Process Analytical Technology

QbD: Quality-by-design

QC: QualityControl

QCD: Quality Control Department

RMSEC: root mean square error of calibration

RMSECV: root mean square error of cross validation

RMSEP: root mean square error of prediction

ROI: Return on Investment

RTR: Real time release

RTRT: Real time release testing

SNV: Standard Normal Variant

USP: United States Pharmacopoeia

UV: Ultra Violet

1 Introduction

1.1 Process analytical Technology (PAT)

The production of pharmaceutical products is generally accomplished batchwise complemented with laboratory tests in order to ensure conformity. This approach has a series of drawbacks. Quality assurance is performed after the product has been manufactured, so increases the batch release time. If nonconformities are found, it is normally difficult to act on process parameters without substantial changes in terms of the production process revalidation. In this case, the irregularities must be identified and explained in a time-consuming investigation, or the out-of-specification material must be thrown away or re-worked. In fact, most manufacturing processes are carried out with fixed process parameters. If the manufacturer wants to make changes in the process towards its optimization during the life of the product, he will need to require a new regulatory submission. The outcome of this situation is the fact that pharmaceutical industry is lagging behind other related industries in adopting new manufacturing technologies which have the potential to improve product consistency, reduce delays in product release and cut overall manufacturing costs. Taking into account the previous considerations, the US Food and Drug Administration (FDA) proposed a new concept: Process Analytical Technology (PAT). PAT can be defined as ”a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and inprocess materials and processes, with the goal of ensuring the final product quality” [1]. PAT is the key element of the ”Pharmaceutical Current Good Manufacturing Practices (CGMPs) for the 21st Century - a Risk Based Approach” initiative announced also by FDA in August 2002 to improve and modernize pharmaceutical manufacturing [2]. PAT has been implemented for years and it is an enabling technology, in the sense that it makes easier the innovation in development, manufacturing and quality assurance by focusing on process understanding and improvement.

1.1.1 Process Understanding

One question that could be asked is: ”What is a process well understood?”.

The answer for this question states that a process is generally considered well understood when:

1. all critical sources of variability are identified and explained;
2. variability is managed by the process and
3. product quality attributes can be accurately and reliably predicted over the design-space established for raw materials, process parameters, manufacturing, environmental, and other conditions.

Making an effort on process understanding allows to lower the burden for validation systems because it gives more options for explaining and qualifying systems that are intended to monitor and control all of aspects of materials and processes.

The best way to improve understanding, optimization, technology transfer and control over the process, it is using experimental design with on-at-in line process analyzers to collect data in real time. The collection of information to enhance process understanding doesn't end when the production is already in place. More information can be gathered during production like

environmental and supplier changes. It is important to put in place the continuous learning of the process over the product life cycle.

1.1.2 PAT tools and principles

PAT tools and principles can offer effective and efficient means for acquiring information to assist process understanding, continuous improvement and development of risk-mitigation strategies. In the PAT framework, these tools can be categorized accordingly to four criteria:

A. Multivariate data analysis

From a physical, chemical, or biological perspective, pharmaceutical products and processes are complex multi-factorial systems. There are many different development strategies available to achieve optimal formulations and process conditions for these systems. The information and the knowledge extracted from these programs can be a huge asset when it consists of scientific understanding of the relevant multi-factorial relationships (e.g., between formulation, process, and quality attributes). We can get this benefit through the use of multivariate mathematical approaches, such as statistical methods, design of experiments, response surface methodologies, process simulation and pattern recognition tools, in conjunction with knowledge management systems.

The pharmaceutical industry commonly uses traditional One-Factor-at-a-Time (OFAT) experiments in the development of the products. This kind of approach doesnt address interactions among product attributes and process variables. To fill this gap, pharmaceutical companies should apply methodological experiments based on statistical principles of orthogonality, reference distribution, and randomization, which can provide effective means for identifying and studying the effect and interaction of product and process variables.

When used appropriately, these tools enable the identification of variables that may be critical to define product quality and process performance. These tools may also identify potential failure modes and mechanisms, and quantify their effects on product quality.

B. Process analyzers

The most common tools used in the pharmaceutical industry consist on simple devices such as those measuring pH, temperature, and pressure in contrast to those that measure chemical composition and physical attributes. The most important advance in this area are process analyzers that can provide measurement of both chemical and physical attributes in a non-destructive way when the materials are being processed. The measurement of these attributes can be made using the following strategies.

- **Off-line:** when the sample is collected and tested in the laboratory.
- **At-line:** when the sample is collected, and analyzed in close proximity to the process stream.
- **On-line:** when the sample is separated from the process stream, and after the analysis returned to the process stream.
- **In-line:** when the sample is analyzed directly in the process stream either invasively or non-invasively.

Most of these process analysis tools (or process analyzers) need multivariate mathematical methods to extract the information needed from complex signatures and to correlate these results to a primary method of analysis.

C. Process monitoring and control

For an effective control of all critical quality attributes, it is important to have a strong link between product design and process development. To achieve this, the PAT framework can include the following steps (the sequence of steps can vary):

- identify and measure critical material and process attributes related with product quality;
- design a process measurement system to allow real-time or near real-time (e.g., on-, in-, or at-line) monitoring of all critical attributes;
- design process controls that provide adjustments to ensure control of all critical attributes and
- develop mathematical relationships between product quality attributes and measurements of critical material and process attributes.

Process monitoring and control strategies have the goal to monitor the process and actively drive it in order to maintain a desired state.

D. Continuous improvement and knowledge management

It's very important the knowledge gathered by continuous learning thought data collection and analysis over the life cycle of the product. With these data, one can justify proposals for post-approval changes. Approaches and information technology systems that support knowledge acquisition from such databases are valuable for the manufacturers and they can also facilitate scientific communication with the regulatory authority [1, 3].

Facing the requirements of PAT tools, there is a need for analytical techniques being able to acquire large amounts of data within seconds during all the critical steps of a pharmaceutical manufacturing process. Examples of these tools include spectroscopic techniques like:

- Near-infrared spectroscopy (NIR)
- Raman spectroscopy
- UV-visible spectroscopy
- Acoustic spectroscopy

1.1.2.1 Infrared spectroscopy

The infrared radiation covers the spectrum from 12800 to 10 cm^{-1} and can be divided into three sections: near, mid and far Infrared (Table1).

Molecular electronic transitions need energy supplied by UV/Visible radiation. Infrared radiation doesnt have enough energy to make electronic transitions. The infrared radiation when absorbed by a molecule may induce vibrational and rotational transitions. For the molecule to absorb infrared radiation, it is necessary a change in the dipole moment during the vibration or rotation. When the electromagnetic radiation interacts with variations in the molecular dipole moment and it has the same vibrational frequency, then will result the absorption of radiation and also variation in the amplitude of molecular vibration [4].

Table 1: The three sections of the infrared region [4].

Region	Wavelength (nm)	Wavenumber (cm^{-1})
Near	0.78 2.5	12800 4000
Middle	2.5 50	4000 200
Far	50 1000	200 10

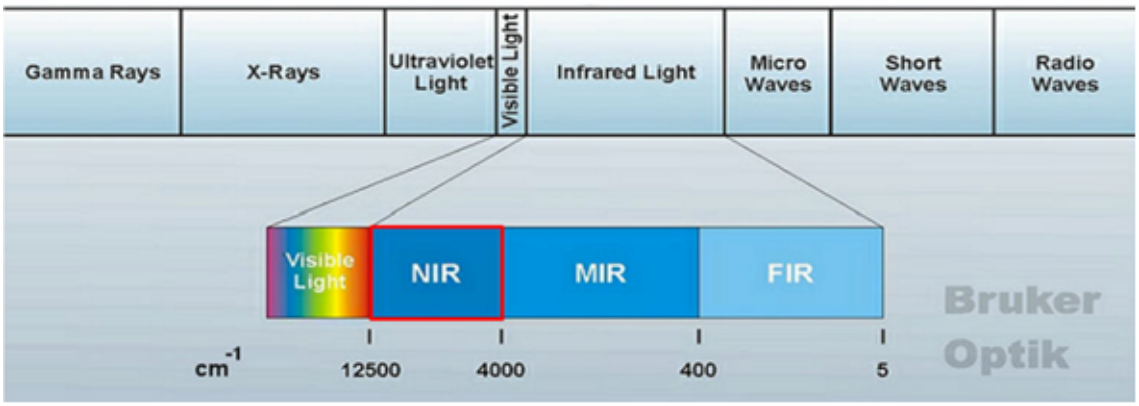

Figure 1: Location of the NIR spectral region in the electromagnetic spectrum (adapted from [5])

1.1.2.2 Near-infrared spectroscopy

This method is based on the near-infrared radiation, between 12500 and 4000 cm^{-1} (Table 1 and Figure1). Compared to mid-infrared, which encompasses the fundamental vibrations, near-infrared radiation has enough energy to induce overtones and combinations of molecular vibrations to higher energy levels. As shown in Figure 2, the overtones absorption are observed in the spectral range between 12500 and 5000 cm^{-1} and combination absorption bands are located between 5000 and 4000 cm^{-1}.

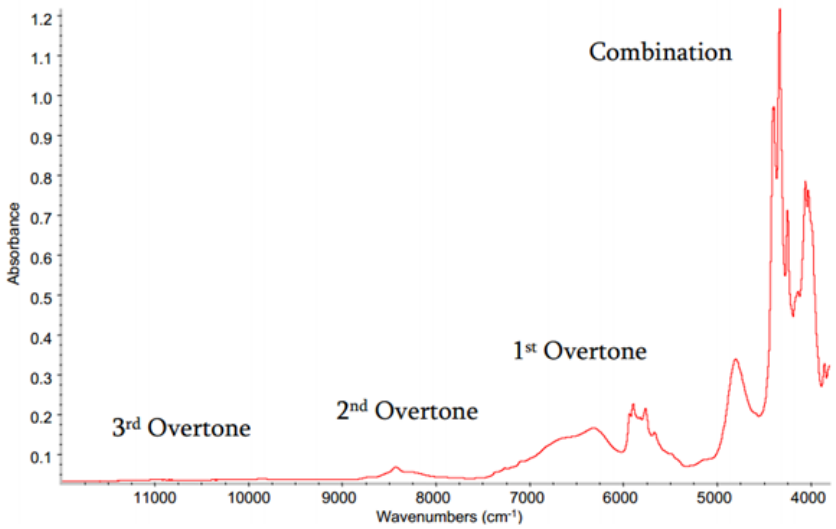

Figure 2: Example of a NIR spectrum with Overtones and combination absorption bands [6]

The absorption of NIR radiation is characterized by overtones and combination. The NIR spectra contain absorbance bands mainly due to four chemical bonds: O-H, C-H, N-H and S-H [7].

1.1.2.3 Near infrared instrumentation

Today, the market offers principally two types of NIR spectrometers: dispersive and Fourier-transform (FT) NIR spectrometers. Figure 3 highlights the differences between disperse and FT instruments in terms of spectral quality. In the spectrum associated to FT instrument (blue line), the absorption line is comparatively sharper than the line of the dispersive instrument (red line).

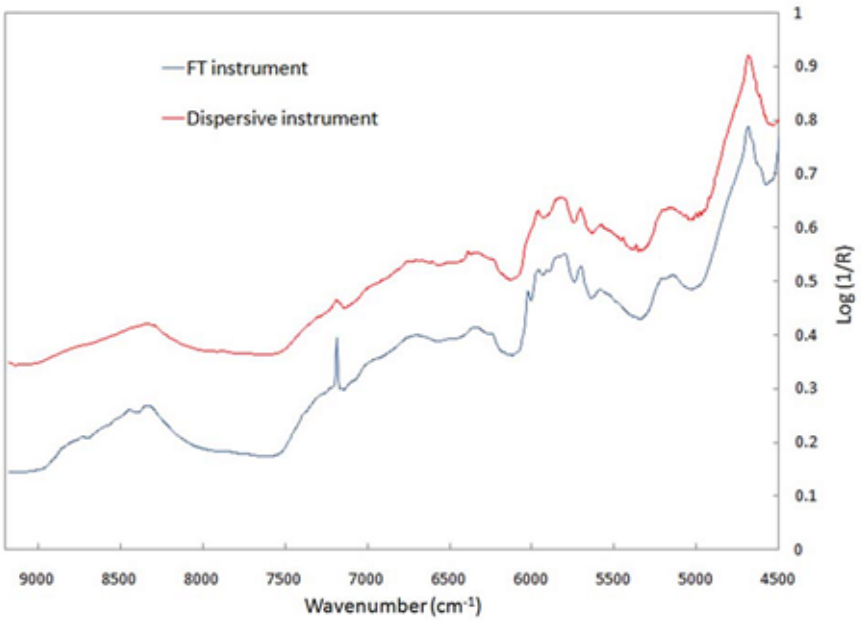

Figure 3: FT and dispersive NIR reflectance spectra of pharmaceutical pellets [8].

By comparison of the technical and physical characteristics of these two type of instruments, FT systems have the major advantages over dispersive systems [7].

- **Multiplex advantage** - The FT instruments have the capability of measure all wavelengths at the same time, as the dispersive instruments can only measure sequentially.
- **Throughput advantage** - In the dispersive instruments, the light reaching the detector is low due to the existence of grating and slits. However these components do not exist in FT instruments then the energy that reach the detector is higher. This offers a huge help with small intensities absorption bands because a higher signal-to-noise ratio is obtained.
- **Conner advantage** - Due to the fact that FT instruments have a moving mirror (in the interferometer) controlled by HeNe laser and dispersive instruments do not, it can get a stable and accurately defined radiation frequency.
- **Stable resolution** While the resolution of FT instruments is stable during the spectrum acquisition, in a dispersive instrument that doesn't happen because resolution is set by selecting the size of the slit.

1.1.2.4 Advantages and disadvantages

The use of NIR in chemical analysis have advantages and also disadvantages. The advantages of this technique are [9]:

- **The sample need minimal or no preparation, and the sample isn't destroyed**

  This gives the possibility to use the right equipment for the right environment and it can directly measure in the manufacturing area at, on or in-line, maintaining the sample intact.

- **Capability of extract multiple sample critical quality attributes with only a single spectrum**

  When a NIR spectrum is obtained, it contains not only chemical information, but also physical information. This technique has the capability of obtaining multi quality attributes non-destructively from the same spectrum. That doesn't happen with other analytical techniques that need specific sample preparation for each quality attribute testing.

- **Fast acquisition time and results**

  The NIR instruments have the capability of obtaining measurements and results within seconds. This offers, when applied as a process analyzer, more information about the manufacturing process than laboratory testing.

- **Environmental friendly and low cost technique**

  Comparatively to liquid chromatography, which is thoroughly used for quality control in the pharmaceutical industry, NIR doesnt use solvents. Consequently, there is a reduction on costs and an healthy environment for workers.

- **Only necessary single calibration for qualitative and quantitative NIR models**

  Re-calibration isnt needed except when the model is updated, which is only necessary when the sample is within specifications and the specter deviates from the calibration set. This type of deviation can be cause by a change in raw material provider or alteration in process parameters.

- **Technology advances in instrumentation**

  Depending of the point and interface of the process, a range of types of probes, fiber length and new technology for example equipment with wireless capabilities and batteries are available.

- **High sensitivity to water**

  This fact can be an advantage when it is pretend to control the moister of the product, but can also be a disadvantage in cases that the water spectrum hide information about others parameters thats pretend to identified and control.

However, this type of technology has disadvantages such as [7]:

- **Difficulty to establish a relation between a molecule and the respective spectrum**

  When compared with other techniques like mid-IR spectroscopy, its difficult to establish

a correlation between the spectrum and molecule. With chemometrics it is possible to correlate spectra with physical and chemical characteristics.

- **NIR calibrations development**

  To develop a calibration for a quantitative NIR model, not only the sample need to be analyzed by NIR, then also by a reference method for example: Liquid chromatography for API content determination or Karl Fischer Titration for moister determination. If some aspects will be expected encountered in the work routine and variations in the sample and/or environmental (temperature, humidity,) can possible interfere with measurements, it will be necessary to integrate the calibration set.

- **Low penetration of the beam into the sample in diffuse reflection mode**

  This fact needs to be considered because some critical variables cant be estimated in this mode. For example, the active substance concentration in tablets.

- **NIR is a relative method**

  To obtain a quantitative NIR model, it will always need a reference method.

- **NIR doesnt have the capability to measure low concentration products**

  The limit of detection of NIR spectroscopy can change from a substance to another. It can be accepted that NIR will not be able to accurately quantify a substance that has a %w/w lower than 0.1%. This makes NIR spectroscopy not suitable for determination of degradation products for instance.

- **Physical characteristics of the sample can change the sample spectrum**

  Changes in physical properties of samples (e.g., particle size) can affect the estimation of other properties. These problems can, sometimes be solved with chemometrics.

1.1.2.5 Development of quantitative NIR models

The European Medicines Agency (EMA) "guideline on the use of near infrared spectroscopy by the pharmaceutical industry and the data requirements for new submissions and variations" [9] describe the methodology to build predictive NIR models. The Figure 4, describe the main stages of this methodology.

After defining the NIR method propose, the next step is to design the set of samples needed for the calibration and finding a suitable analytical reference technique. Indeed, one has to be aware that NIR spectroscopy requires a reference analytical method when quantitative methods are to be developed. Once the calibration is developed the reference method is no longer needed.

Prior to the reference measurements, a NIR spectrum collection is required, since a reference method can have adverse destructive effects on certain sample. The sample size between the reference technique and NIR should also be similar, to minimize any differences spotted. The entire sample set is then split into calibration and validation sets, with the first being used to create a quantitative model while the second is used to test the developed NIR model in an external way.

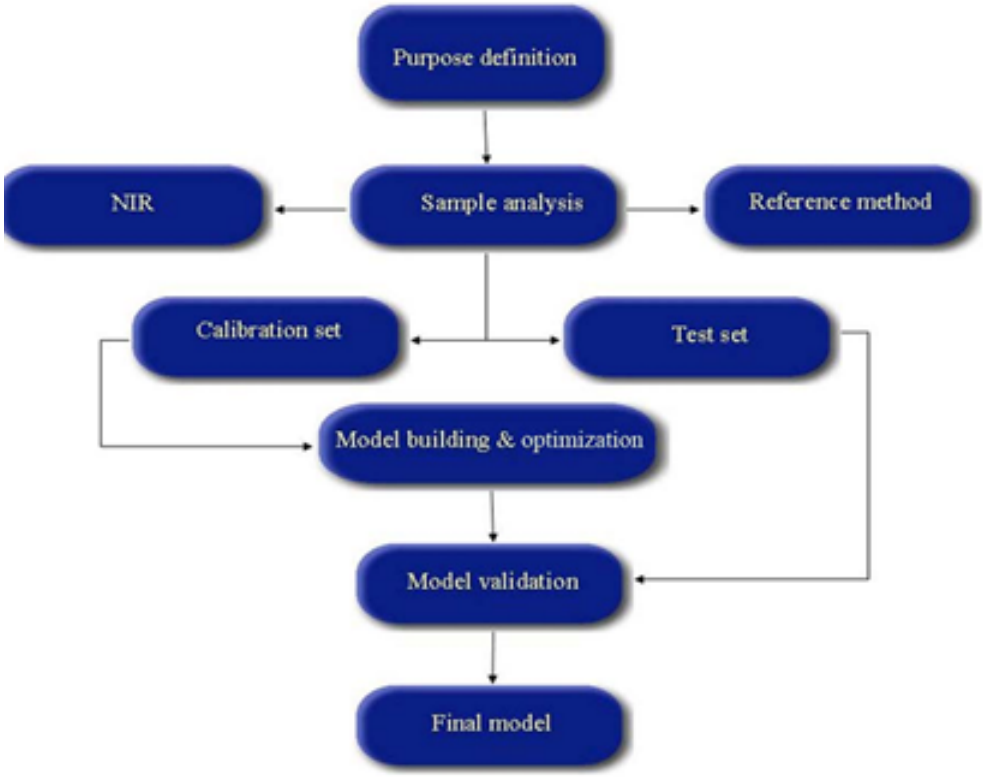

Figure 4: Diagram of the methodology to create NIR predictive models [8].

To obtain a robust model, it is fundamental to quantify future possible variability and include it in the calibration set for that. This accounting for variability happens both in the calibration set as well as the validation set to evaluate the accuracy and robustness of the model. Depending on the manufacturing process of the studied formulation, many sources for variability can be integrated in calibration and validation sets, such as:

- concentration range of the property of interest;
- the raw materials;
- changes between batches;
- a production campaign effect;
- a pilot and industrial batch effect;
- operator effect;
- temperature effect and
- day effect.

The next step is the model selection and optimization. It is usually performed by means of crossvalidation which is a fast and easy way to obtain a first estimation about the model ability to predict samples that were not included in the model calibration. For the development of the model it is important to check two parameters: the root mean square error of calibration

(RMSEC) to verify the capability of the model to fit the data and the root mean square error of cross validation (RMSECV) for evaluation of the model performance.

After the model has been optimized, it is validated with an external validation set. This leads to the calculation of the root mean square error of prediction (RMSEP) which is the same than RMSEC but refers to samples that were never included in the calibration set. Compared to RMSECV and RMSEC, the RMSEP is a true performance indicator of the model as it is calculated with samples that were never included in the calibration set.

If the RMSEP and RMSEC are both low and close to each other, it means that the model is accurate and robust enough. However, if the RMSEP is too high, further optimization is necessary. If the RMSEP is still high after the optimization, one has to investigate the presence of outliers and if enough variability was introduced in the calibration set [9, 10].

1.1.2.6 Raman spectroscopy

Raman spectroscopy was discovered in 1928 by Raman and Krishman [11–13].

Raman spectroscopy belongs to vibrational spectroscopy, like infrared spectroscopy, as it also offers information on molecular vibration. Besides both belonging to the same type of spectroscopy, NIR spectroscopy is based on the absorption and reflection of light, while Raman spectroscopy arises from scattering of light by the vibrating molecules. Two main phenomena, represented in Figures 5, happen when radiation hits a sample:

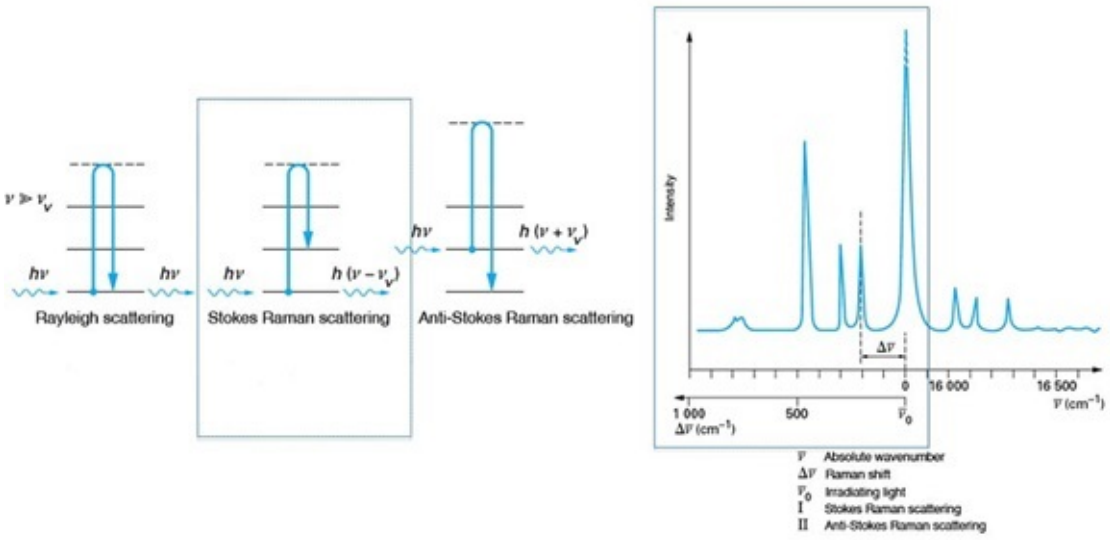

Figure 5: The Raman scattering phenomenon [8].

– The Rayleigh scattering happens when there is no change in the photon frequency, which corresponds to an elastic collision and represents 99.9% of Raman activity.

– Stokes and anti-Stokes Raman scattering happens when there is a change in photon frequency, which corresponds to an inelastic collision. The difference between these two scattering phenomena relies on the photon frequency decrease in the case of Stokes scattering or increase in the case of Anti-Stokes scattering. The Stokes scattering is dominant and represent 0.1% of the Raman activity.

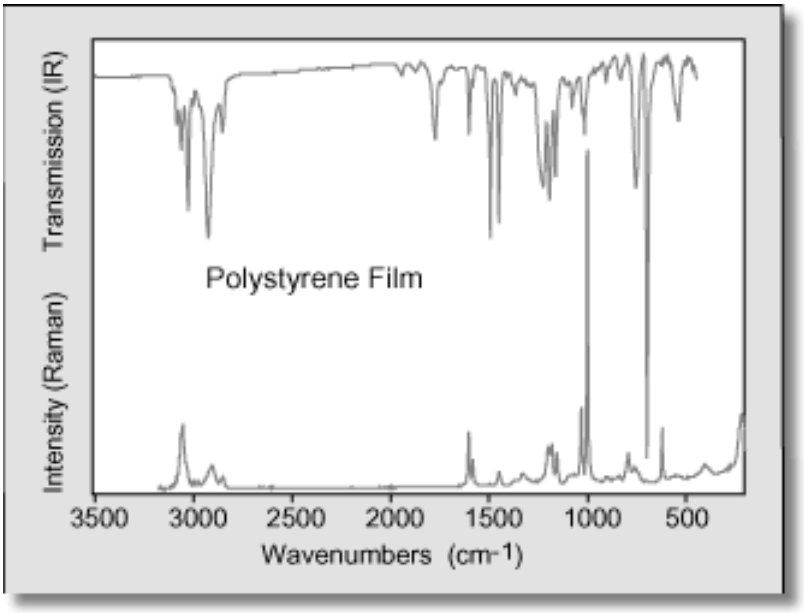

Figure 6: Midinfrared and Raman spectra of a polystyrene film [14].

As can be seen from the MIR and Raman spectra of a polystyrene film presented in Figure 6, high intensity Raman bands usually correspond to low intensity MIR bands. This is due to the fact that a variation of the molecule polarizability is required for the molecule to be active in Raman spectroscopy while it is a variation of the dipole moment that is needed for the molecule to be active in MIR spectroscopy. The fact that these two phenomena cannot possibly occur at the same time, makes MIR and Raman complementary spectroscopic techniques.

1.1.2.7 RAMAN spectroscopy: advantages and disadvantages

The use of RAMAN in chemical analysis, like NIR spectroscopy, have advantages and disadvantages. The advantages of this technique are [12, 13]:

- **Sensitivity to polarizability variations**

  There exist significant differences between RAMAN spectra of common bonds such as CH, CO or OH and molecules with benzene rings (that exist in many APIs), and no overlap between these two groups. Consequently, the intensity of most API bands will be stronger then excipients bands. These facts, make Raman an interesting technique for API evaluation on a pharmaceutical formulation.

- **Require minimal sample preparation**

  Like NIR spectroscopy, Raman spectroscopy offers the possibility for in, on and at-line with or without optical fiber accessories.

- **Analysis of samples in different physical states**

  Raman spectroscopy can analyze sample in gas, liquid and solid state.

- **Low sensitivity to water**

  Comparatively to NIR spectroscopy, RAMAN spectroscopy is blind to water that confers the possibility of samples analysis with high moisture content.

However, this type of technology have disadvantages such like:

- **Affect or totally overwhelmed by fluorescence**

  Non-resonance Raman signals are generally weak and can be easily overwhelmed by fluorescence signals when uses light sources in the visible range. Besides that, fluorescence has a longer excited state lifetime compared to Raman scattering, causing an inability to detect Raman signals.

- **Destructive analytical technique**

  RAMAN spectrometers have strong laser light that can induce alterations or destruction of the sample.

1.2 Analytical method validation

The analytical methods have a lifecycle that contains four major steps that are represented in Figure 7.

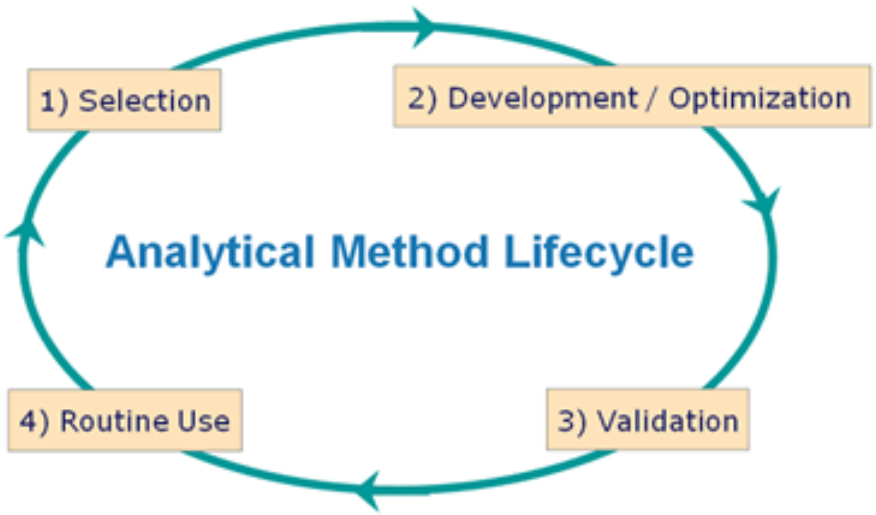

Figure 7: Description of the Analytical Method Lifecycle [8].

The first step is the selection of the appropriate analytical technique for evaluation of the property of interest; the second is the development and optimization of the method; the third is validation the method permitting to test the suitability of the analytical method regarding its purpose: to quantify accurately the property of interest. After the method's validation, it is ready to be used but the lifecycle is dynamic and it isn't finish like is demonstrated in the

Figure 7. Any modification of the method, requires a new validation process (and submission the regulatory authority) before using it in routine conditions again. This isn't entirely truth in the case the analytical method is developed using the design-space approach. In this case, only changes of the model parameters outside the design-space will require a new method validation. This approach is also ICH Q2(R2) [15] compliant as it provides the values of validation criteria such as accuracy, trueness, precision, limits of quantification, range and linearity. This method of development and validation isn't exclusive for NIR spectroscopy, so can be used for guidance to others techniques like RAMAN spectroscopy.

1.3 Real Time Release Testing

Real time release testing (RTR) is defined as "the ability to evaluate and ensure the quality of in-process and/or final product based on process data, which typically include a valid combination of measured material attributes and process controls" [16].

The right way to implement RTR will vary depending on the process requirements, but to have success in the change authorization, it is need to demonstrate the follow [16, 17]:

- That the pharmaceutical development studies have identified the critical quality attributes for the finished product;
- That a risk based development program has been carried out;
- That a scientifically based control strategy has been developed and implemented;
- That the manufacturing process is, or will be, validated adequately (as evaluated on inspection);
- That in process requirements chosen for approval/rejection are decided on the basis of the acceptance criteria defined in the development studies;
- The relationship between end-product testing and RTRT, including justification of acceptance criteria;
- That clear, specified procedures are in place describing the reporting and actions to be taken on approval/rejection;
- That the applied technologies gives an acceptable quality;
- Comparative test results (parallel testing) supporting the relationship between the end-product specification and the RTRT where applicable;
- That the RTRT approach is equivalent to or better than the end product test;
- That a contingency plan in case of equipment failure for example.

The best, easy and fast way to achieve this requirements is use PAT tools such like NIR or RAMAN spectroscopy. In alternative, it can be applied parametric release, which is "based on evidence of successful validation of the manufacturing process and review of the documentation on process monitoring during manufacturing, without direct measurement of quality attributes" [16].The process monitoring is using variable such like temperature, pressure and time for terminal moist heat sterilization.

1.4 Quality-by-design (QbD)

The QbD initiative within the pharmaceutical industry represents a large change initiative supported jointly by industry, academia and regulatory agencies worldwide. The ICH Q8(R2) guideline on pharmaceutical development, defines QbD as: "quality should not be tested into a product, it should be by design" [16]. The design -space concept is also described in this guideline, and defined as "the multidimensional combination and interaction of input variables (e.g., materials attributes) and process parameters that have been demonstrated to provide assurance of quality" [16]. The same ICH guideline indicates that as long as the process and formulation parameters are kept within the defined design-space, no regulatory post approval change is needed. Furthermore, the design-space has others advantages like guaranteeing the reliability and robustness of the process, supporting the quality risk management system. Facing the challenges and expectations of the ICH Q8(R2) guideline on pharmaceutical development, the process analyzers as described in the PAT concept can be advantageously integrated in a general quality-by -design quality system to provide reliable real time information helping to define the process design-space and compliance. Accordingly, this combination of real time analysis together with advanced process understanding and improved quality risk management are clearly promoting factors to achieve consistent product performance as requested by the ICH Q10 guideline on the pharmaceutical quality system [11].

1.5 Pharmaceutical solid forms

The principal pharmaceutical solid forms currently in the market are tablets, hard capsules, soft capsules, granules, powders, cachets, pellets and lozenges [18]. The list encompasses the pharmaceutical solid forms with interest for this study. These forms are coated tablets, hard capsules and pellets.

1.5.1 Tablets

The tablet form is the pharmaceutical form most commonly prescribed. For example, in the United States, 80% of the drugs are formulated for the systematic effects and are produced as oral dosage form [19]. In the group of oral dosage forms, tablets are mostly preferable because of their relativity low cost manufacture, package, shipment and virtual tamper resistance.

Another reason for choosing tablets in comparison with liquids is the fact that each tablet represents a unit dosage form with a precise dosage. The liquid form has a lot of disadvantages compared to tablets such as: they are much more expensive to ship, prone to breakage or leakage, the taste masking normally is a problem, they are less portable and need more space in the shelf, the drugs are more unstable in liquid form and the expiring limit tends to be shorter.

On the other hand, the tablets also have disadvantages. The following items are among these disadvantages [20].

- Some drugs have compression problems related to their amorphous nature or flocculent, and low density.
- It's difficult or impossible to formulate and manufacture some drugs with features or combinations of:
  - Poor wetting
  - Slow dissolution properties

  - Intermediate to large doses

- Sometimes drugs have a bitter-taste, an objectively odor or a sensitivity to oxygen or atmospheric air. In these cases, it's necessary to reformulate or add more steps like coating the tablets or use capsules.

In summary, the pharmaceutical industry prefer tablets because of low cost production process, minimal storage space requirements, compliance of patients and optimum portability.

1.5.1.1 Manufacturing process

Depending of the properties of active pharmaceutical ingredient (API) and the formulation, essentially three types of preparation methods for compaction exist [19–21]:

- Wet Granulation
- Dry Granulation (roller compaction or slugging)
- Direct compression

For the interest of this study, only wet granulation was considered. Additionally, the drying, mixing, compression and coating processes were considered (Figure 8).

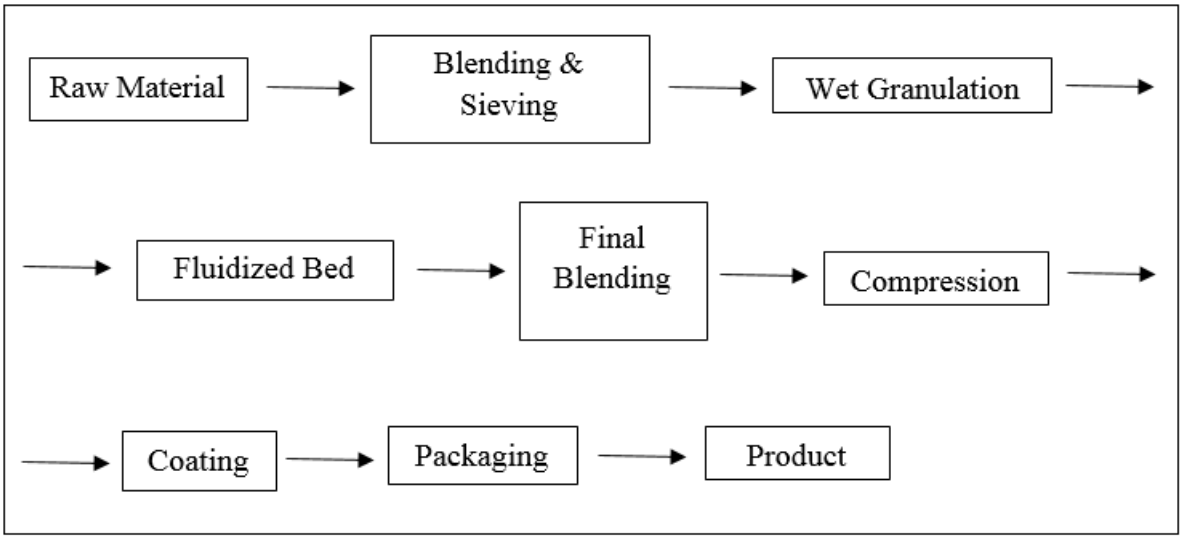

Figure 8: Example of an operations for pharmaceutical tablets manufacturing with wet granulation.

As example of operations leading to a coated tablets manufacturing process with wet granulation are :

- The first step is the weighing out of the various raw materials, including both active ingredients and excipients, into small bins.

- The separate powders are transferred into a single large container and mixed for a set length of time, then sieved. The mixer rotates the container as a whole, as opposed to agitating the powder inside the container.
- Following the initial mixing step, the mixture undergoes wet granulation. In this process, a set quantity of water or granulation liquid is added to the powder to agglomerate the particles. The wet granulate is then dried in a fluidized bed drier. The mixture is then sieved again as described above.
- After granulation, a lubricant is added and the container is mixed once again. Generally, magnesium stearate is used as a lubricant to ensure release of the tablets from the die in the tableting step that follows.
- Following granulation, the powder is transferred to an automatic rotary press which forms tablets by compressing the powder in a die. The rotary press currently has a feedback control system that manipulates the tablet volume in order to control the tablet mass.
- Tablets are coated with a liquid which is sprayed at a low flow rate onto the tablets in a rotating drum. The process relies on a tumbling action of the tablets as the drum rotates to ensure even coating.
- After coating, the tablets are fed into an automatic packaging line and inserted in blister packs.

1.5.2 Capsules

The capsules are defined by the Portuguese pharmacopoeia being ”Capsules are solid preparations with hard or soft shells of various shapes and capacities, usually containing a single dose of active substance. They are intended for oral administration” [22].

In March and December of 1834, two scientists, Mothes and Dublanc, submitted a patent about how to manufacturer a single-piece, olive-shaped, gelatin capsules. The capsule is closed by drooping a concentrated warm gelatin solution above the capsule. Later, in 1848 and patent in England in 1865, James Murdock invented the two-pieces telescoping capsules [20].

The major constituent of capsules is gelatin because of its properties:

- Non-toxic;
- Readily soluble in biological fluids at body temperature;
- Good film forming properties and, as in water and waterglycerol systems.

Two types of capsules exist (type A and B), depending on the raw-material used. Type A uses bone as the principal raw material. This material has the benefit of producing a tough, firm film but it has the inconvenience of tending to be hazy and brittle. The type B uses pork or calf skins as principal component. Normally, it uses pork skin because this gives plasticity and clarity to the blend and also reduce haze or cloudiness in the finished capsule. Other materials can be used to make capsules, like starch [21].

1.5.3 Pellets

The term pellets is defined by pharmaceutical industry as ”small, free-flowing, spherical particulates manufactured by the agglomeration of fine powders or granules of drug substances and excipients using appropriate processing equipment” [21]. The advantages of using this pharmaceutical form, comparing to single-unit dosage forms, are [21, 23]:

- high degree of flexibility in the design and development;
- can be divided into desired dose strengths without formulation or process changes;
- can provide different release profiles at the same or different sites and
- reduced inter- and intra-patient variability.

On the other hand, the pellets also have disadvantages like:

- the volume per dose is high because of its high bulk density;
- specific surface area per dose is higher so more amount of coating should be given and
- preparation of pellets is a complicated and time consuming process

1.5.3.1 Manufacturing process

There is a variety of pelletization techniques base on the application and the requirements of manufacturers (Figure 9). The most commonly used and intensely investigated pelletization processes are powder layering, solution/suspension layering, and extrusionspheronization.

For the interest of this study, only pellets manufacturing with layering with solution/suspension were considered.

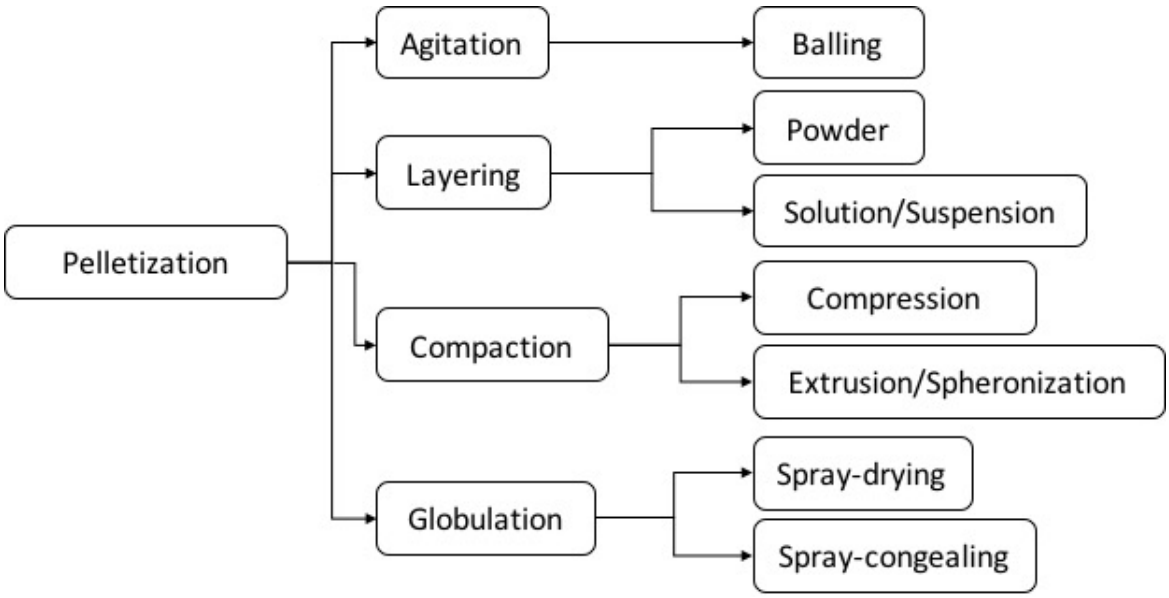

Figure 9: Different pelletization techniques (adapted from [24]).

In the case of pellets manufacturing with the solution/suspension layering method, the growth of pellets involve deposition of successive layers of solution and/or suspension of drug substance and binders on existing nuclei, which may be inert substrate seed, crystal or granule of the same drug. The drug particles are dissolved or suspended in the solvent, with or without binder. Droplets of the binding liquid spread on to the surface of the nuclei. During drying, the liquid evaporates. Then, the dissolved substances crystallize out and capillary forces formed draw the particles towards each other and towards the inert seed, forming solid bridges (Figure 10) [24].

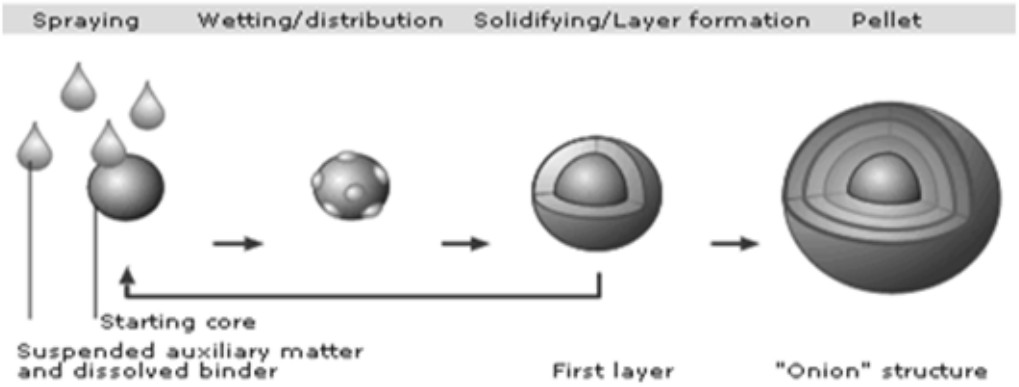

Figure 10: Different pelletization techniques (adapted from [24]).

Some materials that can be used to the starter cores in the production of coated pellets are for example: sugar spheres consisting of saccharides and its derivatives (sugars, sucrose-starch mixtures, oligosaccharides, polysaccharides), microcrystalline cellulose spheres, pure drug crystals, polymers such as plastic resins, inorganic substances (silica glass, hydroxyapalite) or organic substances (activated carbon, acids like citric, fumaric, tartaric, ascorbic acids etc.). [21]

1.6 Implementation of PAT/QbD/RTRt in the pharmaceutical industry

Since 2002, with the initiative announced by FDA, scientific investigation was being made to explore potential applications of PAT tools in the pharmaceutical industry [2]. In 2006, a study identified opportunities for PAT implementation in three products and the corresponding economic impact. The study, not only identified the opportunities in three products, but also proved the economic benefit for implementing this technology in the production area. [25]

The most common case of implementing PAT technology in the manufacturing line involves NIR [26–28] or RAMAN [28–30] spectroscopy in the reception of raw-materials for identification. At MEDINFAR RAMAN spectroscopy is already used for this purpose. There are already a number of successful implementation cases of PAT in the pharma industry worldwide. Some companies that reported these success situations include [31]:

- Sanofi Aventis that got at least 10 product approvals manufacturing products with PAT systems;

- Pfizer reported to have save 4 billion dollars with the implementation of PAT technology and success in approving two product for real time release test in 2009 in EMEA and 2010 with FDA [32];
- GSK saved two billion dollars in inventory;
- Abbot pharmaceutical uses PAT systems to control the Porto Rico plants from US and save three digit million dollars a year in manufacturing and one billion dollars in saving inventory and
- AstraZeneca has implemented this technology in Plackstadt and the manufacturing plant in Sdertlje controlled by PAT (at least for 70% of their products).

Other companies reporting PAT implementatios are Ge Healthcare, Merck, Wyeth, Lilly, Lundbeck, Baxter, Amgen, Novo Nordisk, Watson Pharmaceuticals, Xcellercx, Scherring-Plough, Johnson & Johnson, Amteck, Novartis, Sandoz, Genentech and Biogen possibly among others.

2 Manufacturing process of products X and Y

In this chapter will be analyzed the manufacturing line of drug Product X and Product Y, from raw-material to coating in the case of product X (coated tablets) and product Y (capsules). A similar analysis was made in terms of quality control (QC) and in-process control (IPC) for both products.

These two products have been chosen as case-study in this work mainly because:

- They occupy most unit operations of the solid forms manufacturing line This gives the opportunity to exploit all unit operations in terms of implementation of PAT solutions allowing and evaluation of a possible expansion for other products.
- Both products are stably manufactured The Product X and Product Y have been manufactured for years, so it was possible to gather a lot of information supporting the analysis of possible PAT systems implementation. However, the Product Y was recently transferred to recent facilities.
- Reduction of manufacturing costs Both pharmaceutical products, Product X and Product Y, are stably manufactured, so this gives the opportunity to investigate the possibility of changing the quality control paradigm (from end-testing quality control towards real time release testing).

2.1 Manufacturing process of product X (coated tablets)

The manufacturing process of Product X (coated tablets) and respective equipment, step by step, are shown in Figure 11. These steps will be described below.

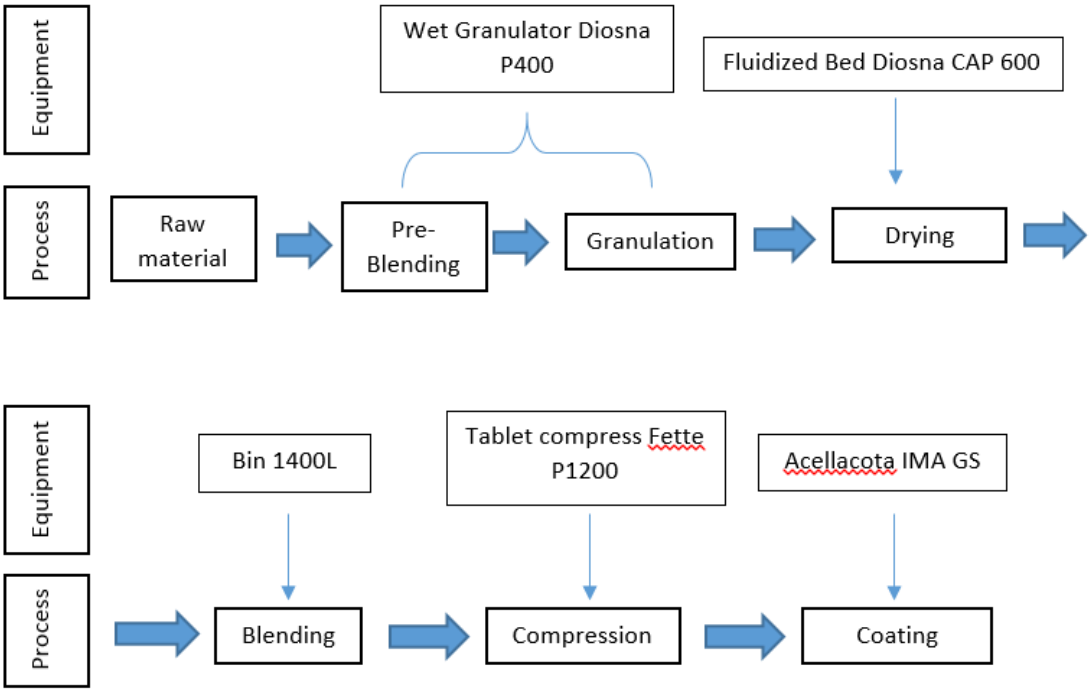

Figure 11: Manufacturing process of product X.

2.1.1 Raw-materials

Raw-materials are identified using a RAMAN TruScan spectrometer. Samples of API are taken for further analysis according to the description in the European Pharmacopeia. When there is an order to start a new batch, the required amount of raw-materials is collected and weighed into small bins. The list of compounds used to manufacture the Product X are described in Table 2 with respective function/application.

Table 2: List of raw-materials needed to manufacture Product X (coated tablets).

Raw-material	**Function**
API (compound X)	Active substance
Corn starch	Filler
Pre-gelatinized starch	Filler/ Disintegrate
Povidone	Binder
Microcrystalline cellulose	Disintegrate
Anhydrous colloidal silica	Gliding
Stearic acid	Lubricant
Red dye (Opagios 2 Red)	Dye

2.1.2 Blending and granulation

Before starting the granulation step, the API and compounds corn starch and pre-gelatinized starch are added to the Diosna P400 (Figure 12) and blended. In this task there is a control of the stirring speed and time. At the same time, the granulation solution is prepared containing the binder and purified water. The wet granulation process then proceeds in the Diosna P400. After this, the product is transferred into a fluidized bed Diosna CAP 600, passing through the milling equipment COMIL U20. (Figure 13) The IPC of these two operations are described in the Table 3.

Table 3: In process control (IPC) of pre-blending and granulation of Product X

Unit Operation	**IPC**
Pre-blending	Time
	Stirring speed
Granulation	Aspect
	Stirring time
	Nozzle opening
	Mixer speed
	Mixer final energy

Figure 12: Wet granulation/blender equipment Diosna P400

Figure 13: Milling equipment COMIL

2.1.3 Drying

After milling, the granules are transferred to the fluidized bed dryer Diosna CAP 600 (Figure 14), where the drying process occurs. Loss on drying (LOD) is evaluated on a Metller moister balance (Figure 15) at the temperature of 60 °Cfor 7 minutes (first sample collected before drying). After 50 minutes of drying a sample is collected and measured again for LOD. If the moisture is higher than 1%, the drying process continues, otherwise the drying process is stopped. The material is left to cool until the temperature achieves a value around 35 °C. After the cooling step, the Product X granules are calibrated on a Frewitt conical calibrator and then transferred to a bin with a volume of 1400L. Besides the IPC control of LOD described earlier, there are other IPC in this unit operation (Table 4).

Table 4: In process control of the drying process of Product X

Unit Operation	**IPC**
Drying	Temperature
	Time
	Humidity of inlet air

Figure 14: Fluidized bed dryer Diosna CAP 600

Figure 15: Mettler moister balance

2.1.4 Blending

After the drying process and calibration of Product X granules, they are transferred to a bin container (Figure 16 with a volume of 1400L and then transported to a connecting room. In this room occurs the blending process divided into two steps. In the first step anhydrous colloidal silica and microcrystalline cellulose are blended for 2 minutes with inversion time of 2 minutes. Next, stearic acid is blended for 3 minutes with an inversion time of 1 minute. In this unit operation, like in the drying process, is collected a sample from the mixer to estimate the LOD (Figure 17). The product inside the bin is distributed into small containers and then transferred to the tableting room.

Beside IPC control of LOD described earlier, there are other IPC methods in this unit operation (Table 5).

Table 5: In process control of the drying process (Product X).

Unit Operation	**IPC**
Blending	Blend time
	Mesh opening

Figure 16: Bin equipment

Figure 17: Bin tumbler equipment

2.1.5 Compression

When the container arrives from the blending room, the tableting machine Fette P1200 is then activated (Figure 18). At the beginning, the parameters of the equipment are selected to meet the follow specifications:

- Tablets aspect
- Mass uniformity
- Diameter
- Tablet thickness
- Hardness
- Disintegration
- Friability

During the tableting process, a tablets sample is sent to the QC department for analysis. A tablets samples are periodically analyzed at IPC for control of the parameters described in the Table 6.

Table 6: In process control of compression process

Unit Operation	**IPC**
Compression	Aspect
	Average,Weight
	Thickness
	Hardness
	Disintegration
	Friability
	Diameter
	Mass Uniformity

Figure 18: Fette P1200 compression

2.1.6 Coating

In this final step, the Product X from the compression room, is coated with a non-functional layer. Four coating suspensions are applied in the product by mixing it with purified water and Opaglos 2 red pigment until homogeneity is obtained. This mixture is filled in the coating equipment Acellacota IMA GS (Figure 19). During the coating process, a sample of 100 tablets are removed periodically to measure the thickness increment. The process is stopped when the tablets coating achieve the right thickness. After cooling the tablets, a sample is collected and sent to the QC Department. Coated tablets are stored in a container and then transported to the packaging site. Besides the thickness incremental control, there are other IPC methods used in this unit operation (Table 7).

Table 7: In process control of Coating process

Unit Operation	**IPC**
Coating	Aspect
	Temperature
	Coating solution consumption
	Drum rotation speed
	Coating increment
	Average mass
	Mass uniformity

Figure 19: Acellacota IMA GS coating equipment

2.1.7 Quality Control

One important part of the manufacturing process is the quality control of the batch, which it is made by the Quality Control Department (QCD). Quality control tests results determine if a batch is approved or rejected. The tablet sample collected during the coating operation will be submitted to a group of tests referred in table X with the respective analytical technique.

2.2 Manufacturing process of Product Y (capsules filled with pellets)

The manufacturing process of Product Y (capsules with pellets), the other product in analysis, is described in Figure 20 with the respective equipment.Each unit operation is described below.

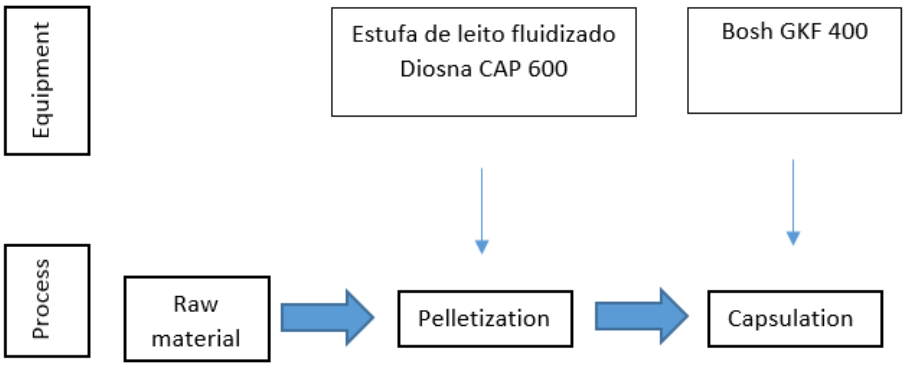

Figure 20: Manufacturing process of product Y.

2.2.1 Raw-materials

The reception of raw-materials is made according to the procedure described for Product X. When the production starts, a required amount of raw-materials is collected and weighed into small bins. The list of compounds used to manufacture the Product Y are described in Table 8 with respective function/application.

Table 8: List of raw-materials for the manufacture of Product Y.

Raw material	**Function**
API	Active substance
Sodium phosphate dibasic dodecahydrate	Buffering agent
Sodium lauryl sulfate	Capsule lubricant; Wetting agent
Anhydrous lactose	Moisture-sensitive drugs, filler and binder
Methylcellulose	Delays the settling of suspensions and increases the contact time of drugs
Hydroxypropyl cellulose	Film-coating and extended-release-matrix former
Diethyl phthalate	Plasticizer
Hypromellose Phthalate (HP-55)	Gastric resistance

2.2.2 Pelletization

This unit operation, pelletization, is divided in three steps, corresponding to the application of three layers. Before the coating process of the first layer, its necessary to prepare the first layer solution. This solution is obtained by preparing two other solutions, one with Methocel E5 and purify water; and other with Klucel and purified water. These two solutions are made a day before to prevent foam to occur.

These two solutions are added to a container, where is also added purified water, sodium lauryl sulfate, anhydrous lactose and the active substance. The first layer solution is freshly prepared. The active substance is added in a dark chamber because it is sensible to day light.

With the first layer solution prepared, the Diosna CAP 600 fluidized bed (Figure 14) is mounted, all parameters of the recipe are confirmed allowing he process to start. The first layer coating process has a run time of approximately 8 hours including the coating and drying

processes. After discharging the first layer cores from equipment, they are calibrated, weighed and then stored into containers without any contact with light or special light.

The second step corresponds to the second layer coating process. The second layer solution contains Methocel E5 and purified water. The second layer coating process initiates after all the parameter are confirmed and the Diosna CAP 600 fluidized bed is mounted. It has a run time of approximately 4 hours including the coating and drying processes. The discharging step of the second layer cores follows the protocol described to first layer cores.

Finally, it's applied a third and last layer on the second layer cores. Hypromellose phthalate (HP-55), acetone and 96% ethyl alcohol are used. When the third layer solution is ready, like before, the equipment is mounted and all the parameters confirmed. The third layer coating process has a run time of approximately 12 hours including the coating and drying processes. The discharge step of the finished pellets follows the procedure described before.

Between the layer coating processes, the Diosna CAP 600 fluidized bed is dismounted and cleaned. The IPC are controlled in each layer and the list of tests is given in Table 9.

Table 9: In process control of pelletization process

Unit Operation	**IPC**
Pelletization	Aspect
	Air outlet temperature
	Inlet air temperature
	Weight
	Humidity of inlet air
	Core temperature
	Spraying pressure
	Pump flow

2.2.3 Capsulation

The capsulation process begins by weighing the pellets, taking into account how much was ordered and the desired concentration of the active substance in the pellets. In the next step, the equipment, the Bosh GKF 400 filling machine (Figure 21) or another similar equipment, is verified and then the following parameters are set:

- Average weight
- Capsules length

When the equipment is ready, the IPC department is warned about the start of the filling process and the parameters referred in the Table 10 are controlled throughout the process. The capsules samples are periodically taken and sent to the QC Department When the capsulation process ends, the capsules are stored into containers and then sent to the packaging line.

Table 10: In Process Control of the capsulation process

Unit Operation	IPC
Capsulation	Aspect / capsules defects
	Filling speed
	Room humidity
	Capsule weight
	Closure/dimension
	Average mass

Figure 21: Bosch GKF 400 filling machine

2.2.4 Quality control

Like was said before, QC tests are an important step of the process, particularly in these two points of the process: after the pelletization process and capsulation process. The collected samples from these two points of the process are sent to QC Department for releasing tests described in Tables 11 and 12.

Table 11: Quality control tests and reference methods of Product Y after the pelletization process.

Tests	Reference methods
Appearance	Visual inspection
API identification	HPLC
Assay	HPLC
Particle size	Sieve and weights
Moisture	Karl Fischer titration
Residual solvents	GC
Dissolutions	HPLC
Gastro-resistance	HPLC

Table 12: Quality control tests and reference methods of Product Y after the filling process.

Tests	**Reference methods**
Appearance	Visual inspection
API identification	HPLC
Assay	HPLC
Particle size	Sieve and weights
Moisture	Karl Fischer titration
Residual solvents	GC
Dissolutions	Value export from analysis report of Product Y after the pelletization process
Gastro-resistance	Value export from analysis report of Product Y after the pelletization process
Uniformity of content	HPLC
Related Substances	HPLC

3 Opportunities for PAT systems implementation

After the identification of the critical process points, a selection of possible implementations of PAT solutions (in this context they will be called opportunities) were proposed in this thesis (Table 13). Each opportunity will follow a similar structure so that they can be read like records:

- Current situation
- Implementation proposal
- Expected improvement
- Requirements
- Problems (or Weaknesses)
- Future applications

Current situation At each opportunity a summary of the current procedures in terms of quality control adopted by the company are described.

Implementation proposal For each opportunity, a detailed proposed of implementation of a PAT system is given. It includes the variables to be monitored (in the sense of quality control), sampling strategy, equipment to use and details a out necessary statistical models and ways of putting in practice the implementation. It is necessary to note that some of the presented proposals are based on literature available data and descriptions, which implies that some modifications might be needed in practice in case of implementation.

Expected improvement Expected improvements of the implementation are presented. A comparison is made with the actual state taking into consideration the major advantages of the proposed implementation.

Operative / Development Requirements At this point, the necessary requirements for the implementation are presented, taking into consideration: the necessary equipment, software, work hours. In Chapter 4 (economic analysis of PAT systems implementation) the expected time for the implementation will be considered, including different scenarios.

Problems (or Weaknesses) Technology and the way it is applied can have intrinsic associated problems as well. For that reason, this opportunity will include potential problems that can arise from the situation change.

Future applications In each opportunity, possible future applications are foreseen in order to capitalize the investment in the equipment/monitoring solution.

Beside the parameter describe before, each opportunity was classified according to 5 criteria, which they are describe as follow:

- Cost/Benefit
- Implementation Risk
- Flexibility

- Expansibility
- Easy implementation
- Validation difficulty

Each one of criteria is measure in a scale from one to five stars, depending of difficulty or risk.(Table 14 to Table 26)

Table 13: Implementation proposal for PAT system in the product X and Product Y production lines

Manufacturing area	**Product**	**Opportunities**
QCD	Product X and Product Y	1) Raman spectroscopy system for raw materials control 2) NIR spectrometer for the QCD
Manufacturing line	Product X	3) Implementation of a NIR spectrometer to monitor the granulator/blender (Diosna P4000) 4) Implementation of a NIR spectrometer on the fluidized bed dryer (Diosna CAP600) for the monitoring of the drying process 5) Implementation of a NIR spectrometer on the bin tumblr (Bin 1400L), 6) Implementation of NIR spectroscopy at-line for the tableting process (Fette P1200) 7) Implementation of NIR spectroscopy to control the coating process (Acellacota IMA GS)
	Product Y	8) Implementation of a NIR spectrometer on the fluidized bed (Diosna CAP600) for pellets production 9) Implementation of NIR spectroscopy at-line for the capsule filler

4 Opportunities

Opportunity 1

Raman spectroscopy system for raw materials control

Current situation

At the raw-materials reception, the APIs might be identified using a RAMAN spectrometer (Truscan, Thermo Scientific). Its a portable device that collects raw-materials spectra while software compares them against a spectral library of spectra to confirm identity. The raw material assay of Product X and Product Y consists in the collection of samples and analysis by potentiometric titration. For each raw material batch, the assay test has an average time of 30 minutes (considering the equipment time) and 30 minutes of analyst occupation. The remaining tests are done according to the Pharmacopea product monography.

Implementation proposal

A replacement of the assay test (potentiometric titration) by RAMAN spectroscopy, ensuring at the same time the identification test is proposed. For the development and validation of this method, existing Raman spectra already collected and respective assay tests will be used. If needed additional samples will be analyzed following the strategy for analytical methods validation [14].

For the collection of spectra, the RAMAN TruScan spectrometer, that already exists, can be used and the reference method is the potentiometric titration. For validation of this method, it will be necessary to follow the procedure described in section 1.2.

After the model validation, they will be added to the interface software for routine analyses (identification and assay). Both Product X and Product Y can be analysed with this strategy.

Expected improvement

- Time reduction with quality control of the raw-material

Problems

- Dispersive RAMAN technology has the capability of quantify these products. However it isnt the best technique for that analysis. As an alternative, it is recommended the use of a FT-Raman spectrometer [33].
- Another problem is the fact that some raw materials are fluorescent, and this can interfere with the RAMAN spectrum.

Operative / Development Requirements

- Thermo Scientific RAMAN TruScan spectrometer (that already exist)
- Working hours include:
  - Sampling
  - Model development (calibrations)

  - Model validation
  - Model implementation

- Software
- Creation of a spectral library
- Number of persons needed: 1
- Submit the alteration in the product registration
- Potentiometric titrator

Future Applications

This spectrometry technique has the capability of identifying and quantifying different polymorphis forms in crystalline materials. [34]

Table 14: Classification of Opportunity 1

Cost/Benefit	★ ★ ★ ★ ★
Implementation Risk	★ ☆ ☆ ☆ ☆
Flexibility	★ ★ ★ ★ ★
Expansibility	★ ★ ★ ★ ★
Implementation Facility	★ ★ ★ ★ ★
Difficulty of the Parameters	★ ☆ ☆ ☆ ☆

Opportunity 2

Adoption of a NIR spectrometer by the Quality Control Department

Current situation

In the QC Department the following certification tests are made:

- Product X
  - Identification HPLC
  - Assay HPLC
  - Dissolution test
  - Related substances HPLC
  - Colorants and preservatives identification TLC
- Product Y
  - Identification HPLC
  - Assay HPLC
  - Dissolution test
  - Dissolution Dessolutor and HPLC
  - Related substances HPLC
  - Microbiological test

Implementation proposal

It is proposed the acquisition of an Antaris MDS II FT-NIR ANALYSER (Thermo Scientific) with the modules:

- Integration sphere
- Transmission
- Optical fiber

For the analysis of solid forms and tablets, it is only necessary the main equipment and integration sphere modules. The reason for adding others modules is the fact that after purchase it is difficult to make modules addition. With these modules the company is able to analyse other samples like liquid (transmission module) or measure samples remotely and inside their own containers (using a probe). Probes to connect to the optical fiber module can be purchased at any time.

Expected improvement

- Capability of models development that cannot be made with equipment existent in the production line
- Reduction time of Quality Control analysis
- Reduction of Quality Control operation costs
- No need to make sample preparation
- Time reduction with new products development

Problems

- If this technique is applied to liquids with high water content, the water bands will saturate the NIR signal preventing adequate meaurements.

Operative / Development Requirements

- Antaris MDS II FT-NIR ANALYSER (Thermo Scientific) with the next modules:
  - Integration sphere
  - Transmission
  - Optical fiber
- Working hours include:
  - Sampling
  - Model development (calibrations)
  - Model validation
  - Models transfer
  - Model implementation
- Software
  - RESULTSTM Software
  - The UnscramblerTM Software (CAMO Software)
- Creation of a spectral library
- Number of persons needed: 1
- Submit the alteration in the product registration
- Potentiometric titrator

Future Applications

Spectrometer is able to be used not only with solid forms but with other forms like liquids, pastes or creams [35].

Table 15: Classification of Opportunity 2

Cost/Benefit	★ ★ ★ ☆ ☆
Implementation Risk	★ ★ ☆ ☆ ☆
Flexibility	★ ★ ★ ★ ★
Expansibility	★ ★ ★ ★ ★
Implementation Facility	★ ★ ★ ★ ★
Difficulty of the Parameters	★ ★ ★ ☆ ☆

Opportunity 3

Implementation of a NIR spectrometer on the granulator/blender Diosna P400

Current situation

The granulator/blender Diosna P400, use for wet granulation, also does the pre-blending process. During the pre-blending process, it is controlled the stirring speed and time. During granulation process is control parameters like the aspect, the stirring time, the opening of the nozzle, the mixer speed and the mixer final energy. When finish, the granules are transfer to the fluidized bed /dryer.

Implementation proposal

In this operation unit, we can identify the follow CQA:

- Blending uniformity
- Mean particle size
- End-point of the granulation

To estimate these attributes, it is suggested the use of a Series 400 reflectance probe attached to the looking cover on the outside. An optic fiber will be connected to the probe and an ANTARIS MX PROCESS NIR detector which process signal send the NIR spectra to a computer. This equipment offers the possibility to attach up to four probes. Next it will be described, a possible way of development and validation of models for each parameter analysis.

Blending Uniformity

The first step of granulation is the pre-bending and it is important to control the blending uniformity and the simple way to do that is to verify the standard deviation of NIR spectra of all compounds until reaching the minimal value possible kept stable over time. For the development of the model, it is suggested to follow the procedure described by Krishel Naicker and Gareth Kilian (2007) [36] or Peter J. Brush and Albert W. Alexander (2006) [37].

Mean particle size

An important parameter that can influence the quality of the granules is the mean particle size. Jukka Rantanen et al. (2005) [38] and Pirjo Luukkonen et al. (2007) [39] reported the capability of in-line NIR instrumentation with multi-variable analysis for prediction of mean particle size. The previous studies recommend taking as references for model development and

the reference method can be a variety type of meshes or laser diffraction particle size analyzer (Beckman Coulter, LS 230, USA).

After the development and validation process, the model is added to the interface software of the equipment allowing the determination of the time to finish the pre-blending and granulation processes.

It will be necessary to create a new database of spectra for quantitative models, so that it is possible to trace each product batch for inspection and models update.

Expected improvement

- Improvement of process control and understanding
- Improvement of problem detection during the granulation process
- Opening the possibility for quality improvement of granules
- Reduction of batch rejection due to problems in the granulation process

Problems

- Water in high content during granulation may reduce the precision in particle size estimations.
- In case of NIR probe is placed on the inspection window or inside the granulator, exist the possibility of a layer of fines cover the window surface or the NIR probe and have false readings [40].

Operative / Development Requirements

- Thermo Scientific ANTARIS MX PROCESS spectrometer
- Optic fiber
- Working hours include:
  - Sampling
  - Model development (calibrations)
  - Model validation
  - Models transfer
  - Model implementation
- Software
  - RESULTSTM Software
  - The UnscramblerTM Software (CAMO Software)
- Creation of a spectral library
- Number of persons needed: 1
- Submit the alteration in the product registration

- Sieves / laser diffraction particle size analyzer (Beckman Coulter, LS 230) as a reference method

Future Applications

In the future, is possible to predict hardness from tablets from granulation process data [39].

Table 16: Classification of Opportunity 3

Cost/Benefit	★ ★ ★ ★ ★
Implementation Risk	★ ★ ★ ☆ ☆
Flexibility	★ ★ ★ ★ ★
Expansibility	★ ★ ★ ★ ★
Implementation Facility	★ ★ ☆ ☆ ☆
Difficulty of the Parameters	★ ★ ★ ☆ ☆

Opportunity 4

Implementation of a NIR spectrometer on the fluidized bed /dryer Diosna CAP600 for Product X drying process

Current situation

The granules are calibrated, while being transferred into the fluidized bed / dryer Diosna CAP 600. In this equipment, the granules are dried and during this process are controlled the product temperature and humidity of inlet air. When the process ends, a sample is collected and analyzed by LOD. If the moisture content is adequate, the process is stopped. If not, it will continue until an adequate moisture content is achieved. Besides moisture level, it is also controlled the material visual appearance.

After cooling, granules are calibrated on a Frewitt conic sieve and transferred into a Bin 1400L.

Implementation proposal

In this unit operation, it is important to control the water content over the drying process. It is proposed the attachment of Viavi MicroNIR PAT-W, which communicates, via wireless, to a computer. Beside this characteristic, this equipment runs with battery, which can also be used in the blending process (Opportunity 5) and pellets production (opportunity 8). For attachment of the equipment it is needed a Micro PAT Extended Probe accessory with 10cm to measure inside the fluidized bed/dryer Diosna CAP600. These accessories give the possibility of main equipment detachment without cleaning. For the sampling plan, it is proposed a structure described in table 17 [41, 42].

Table 17: Example of sampling plan for development of moister measurement model with NIR in fluidized bed /dryer Diosna CAP600

Time between each NIR measurement	30 seconds
Number of scans per spectrum	32 scans
Time period between samples	60 seconds

The samples will be analyzed by Karl-Fisher test as the reference method. For validation purposes, it will be necessary to follow the procedures describes in section 1.2. After the development and validation process, the model is added to the software for routine operation (drying end-point and percentage of moisture content). It will be necessary to create a new spectral for quantitative models development, so that it is possible to trace each product batch for inspection and models update.

Expected improvement

- It is not needed the current IPC during the drying process
- Elimination of process waiting time (while moisture is being verified)
- Continue process control
- Precision in the end-point of dryer process definition

- Not needed any sample collection

Problems

- Attaching a probe inside the Fluidized bed /dryer Diosna CAP600 might influence the drying process. It will need a cleaning protocol and it may be a source of contamination. As alternative, the NIR equipment can make the measurements through a glass window but this can also hold problems. The window can be covered by some sticky product hampering the adequate monitoring of the processed material [38].

Operative / Development Requirements

- Viavi MicroNIR PAT-W with follow accessories
  - Micro PAT Extended Probe accessory
- Working hours include:
  - Sampling
  - Model development (calibrations)
  - Model validation
  - Models transfer
  - Model implementation
- Software
  - MicroNIR PAT control software (Viavi)
  - The UnscramblerTM Software (CAMO Software)
- Build a spectra database
- Number of persons needed: 1
- Submit the alteration in the product registration
- Karl-Fischer test as a reference method

Future Applications

In the future it is possible to predict the mean particle size of the granules and granules API content [41].

Table 18: Classification of Opportunity 4

Cost/Benefit	★ ★ ☆ ☆ ☆
Implementation Risk	★ ★ ☆ ☆ ☆
Flexibility	★ ★ ★ ★ ★
Expansibility	★ ★ ★ ★ ★
Implementation Facility	★ ★ ★ ☆ ☆
Difficulty of the Parameters	★ ☆ ☆ ☆ ☆

Opportunity 5

Implementation of a NIR spectrometer in the Bin 1400L

Current situation

After drying the granules, these are calibrated and transferred into the Bin 1400L. In this stage besides the granules, are added calibrated microcrystalline cellulose an colloidal silica. In this process it is controlled the mixing time, inversion time and mixer velocity.

After the mix, it is added vegetal striate acid and initiated the second mixing. In this second stage of the process, it is controlled the same parameters as before. When the process finishes, the visual inspection and moisture (Karl-Ficher and LOD techniques) are done.

Implementation proposal

During the blending process, it is important to control the blending uniformity and moisture. For that, it is suggested the use of the same equipment described in opportunity 4. The difference is the attachment to the bin of a MicroNIR PAT Standard Lid Mount Kit for coupling the NIR spectrometer. These accessories give the possibility of main equipment detachment without cleaning.

Blending Uniformity

To verify the blending uniformity it is recommended to follow the procedure describe in the opportunity 3 The validation process will necessary to follow procedure describe in section 1.2.

Water Content

For this parameter it is only need to follow the procedure and sampling plan describes in opportunity 4. After the development and validation of calibration models, these models are added to the control software and will be possible to determine the end-point of the blending process.

Expected improvement

- IPC is strongly reduced
- Probable reduction of the blending time
- Blending end-point determination
- No samples collection

Problems

- It requires the attachment of the NIR equipment in the right place to make sure that the equipment acquires spectra adequately [43].

Operative / Development Requirements

- Viavi MicroNIR PAT-W with follow accessories
  - MicroNIR PAT Standard Lid Mount Kit
- Working hours include:
  - Sampling
  - Model development (calibrations)
  - Model validation
  - Models transfer
  - Model implementation
- Software
  - MicroNIR PAT control software (Viavi)
  - The UnscramblerTM Software (CAMO Software)
- Build a spectra database
- Number of persons needed: 1
- Submit the alteration in the product registration
- Karl-Fischer test as a reference method

Future Applications

Nothing relevant.

Table 19: Classification of Opportunity 5

Cost/Benefit	★★☆☆☆
Implementation Risk	★★☆☆☆
Flexibility	★★★★★
Expansibility	★★★★★
Implementation Facility	★★★★★
Difficulty of the Parameters	★☆☆☆☆

Opportunity 6

Implementation of NIR spectroscopy at-line to monitor the tableting machine Fette P1200

Current situation

After the final blending, the Fette P1200 tableting machine is adjusted taking account the follow parameters:

- Tablet aspect
- Average mass
- Mass uniformity (twenty tablets)
- Diameter
- Hardness
- Thickness
- Disintegration time
- Friability

During the compression, the same parameters are monitored.

Implementation proposal

NIR spectroscopy allows the monitoring at-line of the following parameters:

- Assay
- Hardness
- Disintegration time
- Friability

The NIR equipment recommended for this task is the Thermo Scientific Antaris II, with an auto sampling accessory for tablets with thirty positions. This equipment will be located in the IPC room and the tablets will be send from compression room to here.

Assay

For building a model for Product X assay, it is necessary a sample plan with a minimum of three variations of the API concentration, for example 80%, 100% and 120% (table 20) and take in account another type of factors can influence this parameter for example raw material. These batches need to be made in the laboratory or pilot-scale equipment [**?**, 44, 45].

The samples will be analyzed by HPLC as a reference method. For the validation process, it will be necessary to follow the procedure described in section 1.2.

Hardness

To calibrate a model for harness base on NIR spectra the variations reported in Table 21 are proposed [46].

Table 20: Example of the sampling plan for development of assay measurement model

Variability source	Levels of variability	
	Calibration Set	Validation set
API concentration	3 (80, 100, 120 % of API)	3 (80, 100, 120 % of API)
Number of samples	20	20
Number of scans per sample	32	32

Table 21: Example of sampling plan for development of hardness measurement model with NIR in Fette P1200 compress machine

Variability source	Levels of variability	
	Calibration Set	Validation set
Hardness	3 (5 kp, 7 kp, 9 kp)	3 (5 kp, 7 kp, 9 kp)
Number of samples	20	20
Number of scans per sample	32	32

The samples will be analyzed by the hardness technique described in the Portuguese Pharmacopea IX as a reference method.

Disintegration time and Friability

Disintegration end point is not precise because it is left to the judgment of the operator and is defined as ”that state in which any residue of the unit, except fragments of insoluble coating or capsule shell, remaining on the screen of the test apparatus or adhering to the lower surface of the discs” [47].

It is suggested to follow the procedure described by Aude Pestieau et al (2014) [48] for the development of the models for disintegration time and friability.

Expected improvement

- Possibility of improvement of the quality of tablets
- Reduce the operative costs
- Optimization of the compression process
- Reduction of lots rejected due to problems in the compression
- Reduction of the time/expenses in the quality control

Problems

- Some uncertainty exist about the precision and accuracy of NIR-based models for some of the mentioned parameters, especially friability.

Operative / Development Requirements

- Thermo Scientific Antaris II with follow accessories:
  - Auto sampling with thirty positions
- Working hours include:

  - Sampling
  - Model development (calibrations)
  - Model validation
  - Models transfer
  - Model implementation
- Software
  - RESULTSTM Software
  - The UnscramblerTM Software (CAMO Software)
- Build a spectra database
- Number of persons needed: 1
- Submit the alteration in the product registration
- Karl-Fischer test, HPLC, hardness test, friability test, disintegration test as a reference methods

Future Applications

Possibility to foresee the dissolution profile of tablets [49].

Table 22: Classification of Opportunity 6

Cost/Benefit	★ ★ ★ ★ ★
Implementation Risk	★ ★ ★ ★ ☆
Flexibility	★ ★ ★ ★ ★
Expansibility	★ ★ ★ ★ ★
Implementation Facility	★ ★ ☆ ☆ ☆
Difficulty of the Parameters	★ ★ ★ ★ ★

Opportunity 7

Implementation of NIR spectroscopy in the coating machine Acellacota IMA GS

Current situation

In this final step, the Product X tablets from the compression room, are coated with a non-functional layer. Four coating suspensions are prepared with purified water and pigment. These suspensions are mixed until homogeneity. In the next stage of the coating process, the tablets batch is divided in fractions and pre-heated. When it arrives at the intended temperature, the coating starts with the suspension prepared before. During this process, it is controlled the coating increment comparatively with initial weight.

When finish, the coated tablets are cooled and transferred to the packaging line.

Implementation proposal

At this point of the process it is necessary to control the thickness of the coating layer. For that, it is suggested the use of a Series 400 reflectance probe attached to the arm inside the coating machine nearby the spraying nozzle (Figure 22). An optic fiber connecting the probe to an ANTARIS MX PROCESS NIR detector is required. This equipment is the same used in the opportunity 3. For sampling, the plan presented in Table 23 is proposed [50].

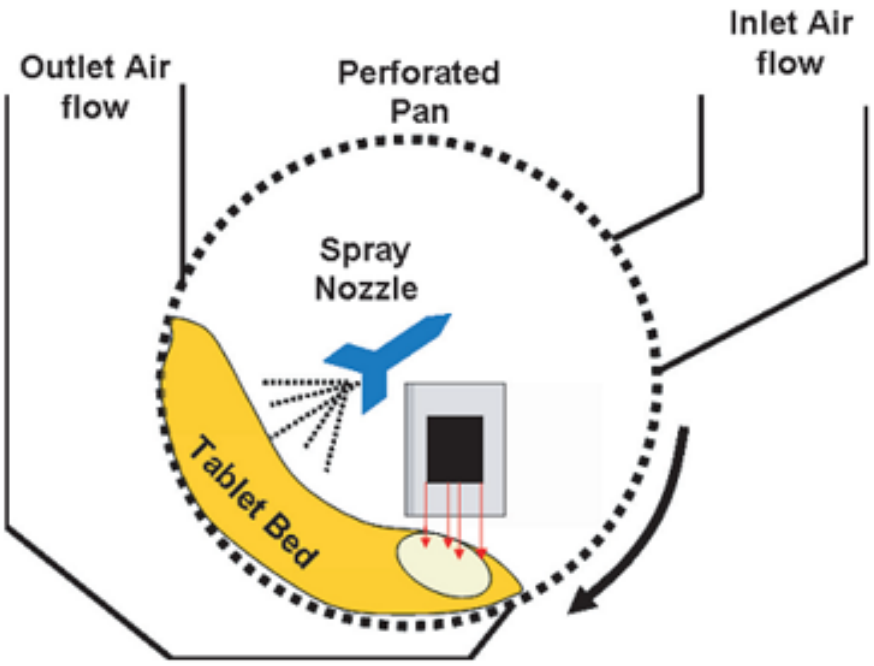

Figure 22: Side-vented pan coater and diffuse reflectance NIR for thickness measurement [48]

The samples will be analyzed by a digital micrometer as a reference method, where is verified the coating thickness. For validation process, will be necessary to follow procedure described in section 1.2.

Table 23: Example of sampling plan for development of thickness measurement model with NIR in Acellacota IMA GS coating machine

Average time for each spectrum collection	20 seconds
Time between samples collection	20 minutes

After the development and validation process, the models are added to the interface software of the equipment and will be possible determine the end-point of the process by measurement in line the coating thickness.

Expected improvement

- The coating thickness is controlled with precision;
- Monitoring in real-time;
- No samples collection

Problems

- The NIR probe will be close to the spraying nozzles. There exists the possibility of NIR measurements from the coating suspension.

Operative / Development Requirements

- Series 400 reflectance probe
- Thermo Scientific ANTARIS MX PROCESS detector
- Optic fiber
- Working hours include:
  - Sampling
  - Model development (calibrations)
  - Model validation
  - Models transfer
  - Model implementation
- Software
  - RESULTSTM Software
  - The UnscramblerTM Software (CAMO Software)
- Build a spectra database
- Number of persons needed: 1
- Submit the alteration in the product registration
- Digital micrometer as a reference method

Future Applications

Not anticipated.

Table 24: Classification of Opportunity 7

Cost/Benefit	★★☆☆☆
Implementation Risk	★★★☆☆
Flexibility	★★☆☆☆
Expansibility	★★☆☆☆
Implementation Facility	★★★☆☆
Difficulty of the Parameters	★★★★☆

Opportunity 8

Implementation of a NIR spectrometer on the Fluidized bed Diosna CAP600 for Product Y pellets production

Current situation

The Pelletization, is divided in three steps, which correspond an application of three layers. In each layer is control de follow parameters:

- aspect
- air outlet temperature
- Inlet air temperature
- weight
- Humidity of inlet air
- Core temperature
- Spraying pressure
- Pump flow

Between each layer, the equipment is demount and clean. When finish the coating of all layers, the pellets are transfer to the capsule filling room.

Implementation proposal

At this stage he following attributes are monitored: Assay Water content Thickness of the layers and dissolution The NIR equipment recommended for this task is the same equipment and accessories described in the opportunity 4 (Viavi MicroNIR PAT-W and the Micro PAT Extended Probe accessory with 10cm).

Assay

For building a model for Product Y assay, like opportunity 6, it is necessary a sample plan with a minimum of three variation of the API concentration, for example 80%, 100% and 120% (Table 25). It is recommend to follow the work do by Jrme Mantanus et all (2010) [51], about assay prediction in pellets and validation of the models.

The samples will be analyze by HPLC as a reference method, where is verified the range concentration of Product Y pellets. For validation process, will be necessary to follow procedure describe in section 1.2.

Water content

The water content is important parameter to control during the palletization process. Because of that, it is recommended to use the procedure describe by Andrey Bogomolov et all (2010) [52]. They had success to predict the moisture in-line during a palletization process.

Table 25: Example of sampling plan for development of assay measurement model with NIR for Product Y pellets in Diosna CAP600 Fluidized bed

Variability source	**Levels of variability**	
	Calibration Set	**Validation set**
API concentration	3 (80, 100, 120 % of API)	3 (80, 100, 120 % of API)
Number of samples	20	20
Number of scans per sample	32	32

The samples of pellets will be analyze by Kael-Fisher test as a reference method, where is verified the percentage of moister content in the pellets. For validation process, will be necessary to follow procedure describe in section 1.2.

Thickness of the layers and dissolution

The thickness of the three layers of the pellets is an important factor to be controlled because may influence many factors like the assay, the gastro-resistance and dissolution profiles of the pellets. Due to this fact it is suggested to use the work do by Alexey L. Pomerantsev et al. (2011) [53]. They shoed that it is possible to predict the thickness of the pellet layers and with this information, they can predict the dissolution or the coated pellets.

The samples will be analyzed by a digital micrometer as a reference method.

After the development and validation of the NIR-based method, the models are added to the interface software of the equipment allowing the determination the end-point of the process by measuring in-line the water content, concentration of Product Y, thickness of the layers and dissolution.

It will be necessary to create a new data base of spectra for quantitative models, so that it is possible to trace each product batch for inspection and models update.

Expected improvement

- More control of the process
- Possibility of improvement of the pellets quality
- To reduce the operative costs
- Reduction of rejected batches due to problems in the pelletization process
- Reduction of quality control time/expenses
- No samples collection

Problems

- The same problem identified in the opportunity 4.

Operative / Development Requirements

- Viavi MicroNIR PAT-W with follow accessories
  - Micro PAT Extended Probe accessory

- Working hours include:
  - Sampling
  - Model development (calibrations)
  - Model validation
  - Models transfer
  - Model implementation
- Software
  - MicroNIR PAT control software (Viavi)
  - The UnscramblerTM Software (CAMO Software)
- Build a spectra database
- Number of persons needed: 1
- Submit the alteration in the product registration
- Karl-Fischer test, HPLC, Digital micrometer as a reference methods

Future Applications

Improvement of the pelletization process.

Table 26: Classification of Opportunity 9

Cost/Benefit	★ ★ ★ ★ ★
Implementation Risk	★ ☆ ☆ ☆ ☆
Flexibility	★ ★ ★ ★ ★
Expansibility	★ ★ ★ ★ ★
Implementation Facility	★ ★ ★ ☆ ☆
Difficulty of the Parameters	★ ★ ★ ★ ☆

Opportunity 9

Implementation of NIR spectroscopy at-line for Product Y capsules filling

Current situation

The capsulation process begin with Product Y pellets weighing taking into account how much was ordered and the concentration of Product Y in the pellets. A Bosh GKF 400 filling machine is used by setting the following parameter:

- Average weight

When the equipment is ready, the IPC department is warned IPC bout the start of filling and the filling parameters refer are controlled throughout the process. Capsule are samples periodically and send to the quality control department.

Finishing the capsulation process, the capsules are stored on a container and sent to the packaging line.

Implementation proposal

Since more than one filling machine can work at the same time, it is suggested the NIR spectrometer Thermo Scientific Antaris II, with the same accessories that were described for opportunity 6. It is proposed to control the following parameter:

- Assay

Assay

To verify this parameter, it is recommend to follow the work made by Ahmed Badr Eldin et all (2015) [54] for building the models. They development them to predict the concentration of Cefixime through a capsule. The samples will be analyze by HPLC as a reference method, where is verified the range concentration of Product Y inside the capsules. For validation process, will be necessary to follow procedure describe in section 1.2.

After the development and validation process, the models are added to the interface software of the equipment and will be possible determine the concentration and identified the Product Y inside the capsules.

Expected improvement

- Reduction of the analysis time
- No sample preparation
- Reduction of the time/expenses in the quality control

Problems

- The shell color can induce light scattering and interferer with the NIR spectrum [49].

Operative / Development Requirements

- Thermo Scientific Antaris II with follow accessories:
  - Auto sampling with thirty positions
- Working hours include:
  - Sampling
  - Model development (calibrations)
  - Model validation
  - Models transfer
  - Model implementation
- Software
  - o RESULTSTM Software
  - The UnscramblerTM Software (CAMO Software)
- Build a spectra database
- Number of persons needed: 1
- Submit the alteration in the product registration
- HPLC as a reference method

Future Applications

Expand this technology and analysis to other pharmaceutical solid forms.

Table 27: Classification of Opportunity 8

Cost/Benefit	★ ★ ★ ★ ★
Implementation Risk	★ ★ ☆ ☆ ☆
Flexibility	★ ★ ☆ ☆ ☆
Expansibility	★ ★ ★ ★ ★
Implementation Facility	★ ★ ★ ★ ★
Difficulty of the Parameters	★ ☆ ☆ ☆ ☆

4.1 Real Time Release

In the case of implementing all the opportunities cited previously, the production line will have more control over the chemical and physical characteristics of the raw material (API and excipients), final pharmaceutical form and changes through the manufacturing process. The ability to collect in real-time this information approached the manufacturing line to the possibility of adoption Real Time Release testing (RTRT).

Tables 28 and 29 provide a comparison between the conventional QC release testing use by the company and the Real Time Release testing proposed with the implementation of the opportunities describe before for both products. In case of impurities test in both products, it will not be necessary to have a routine control because there will be a control of raw materials (API and excipients) as well as all critical points for this parameter identified in the risk analysis of products. The same concept is applied to the microbial quality control and residual solvents test existent in the Product Y release tests.

Table 28: Conventional QC Release Testing Vs Real Time Release Testing for Product Y

Methods for conventional QC Release,Testing	**Methods for Real Time Release,Testing**
Appearance (Visual)	Appearance (Visual)
Identity (HPLC)	Identity (NIR)
Assay/CU (HPLC)	Assay/CU (NIR)
Acid/Base Dissolution (Dissolution Tester)	Acid/Base Dissolution (NIR)
Impurities (HPLC)	Not tested routinely
Microbial Quality (Microbiology)	Not tested routinely
Residual Sovents,(GC)	Not tested routinely

Table 29: Conventional QC Release Testing Vs Real Time Release Testing for Product X

Methods for conventional QC Release,Testing	**Methods for Real Time Release,Testing**
Appearance (Visual)	Appearance (Visual)
Identity (HPLC)	Identity (NIR)
Assay/CU (HPLC+ Weight)	Assay/CU (NIR + Weight)
Base Dissolution (Dissolution Tester)	Base Dissolution (NIR)
Impurities (HPLC)	Not tested routinely
Dyes Identification (TLC)	Not tested routinely
Average Mass (weighing-machine)	Average Mass (weighing-machine)

5 Economic analysis

The previous chapter presented the opportunities of PAT systems with a target of real time release, covering the control of raw materials and end product and monitoring the solid forms production line especially the unit operations: wet granulation, drying, blending, tableting, coating, pelletization and capsule filling.

This chapter describes in detail the business impact of the full PAT system implementation on the manufacturing process of Product X and Product Y. A variety of factors were considered for the economic analysis. First, the sites production data will be analyzed with focus on manufacturing time, batch production and quality control cost. Next, an analysis of implementation costs including investment in equipment, models development and validation cost. Finally, it will be presented a cost-benefit analysis considering the whole implementation.

5.1 Product X and Product Y manufacturing data analysis

5.1.1 Manufacturing time and batch production analysis

To make easy the analysis of current manufacturing time and for subsequent economic analysis, the following factors were taken into account:

- quality control tests for one batch of each product are made one at a time by one analyst and
- the manufacture of one batch begin when the other finish.

Figure 23, shows the manufacturing time line of Product X with and without implementation of PAT systems. It can be observed that IPC Control occupies a small portion of all time of the process. On the other hand, quality control occupy a large portion of the total time. With PAT, time needed for IPC of drying and blending process and quality control are almost suppressed, which allows a time saving of 51% comparatively to the current process situation.

Figure 24, describes the manufacturing process of Product Y with and without PAT. It can be observed that the quality control of Product Y occupies a large portion of the of manufacture time line. With the implementation of PAT, it is possible to eliminate most quality control burden representing an approximate time saving of 66% comparatively to the current process situation.

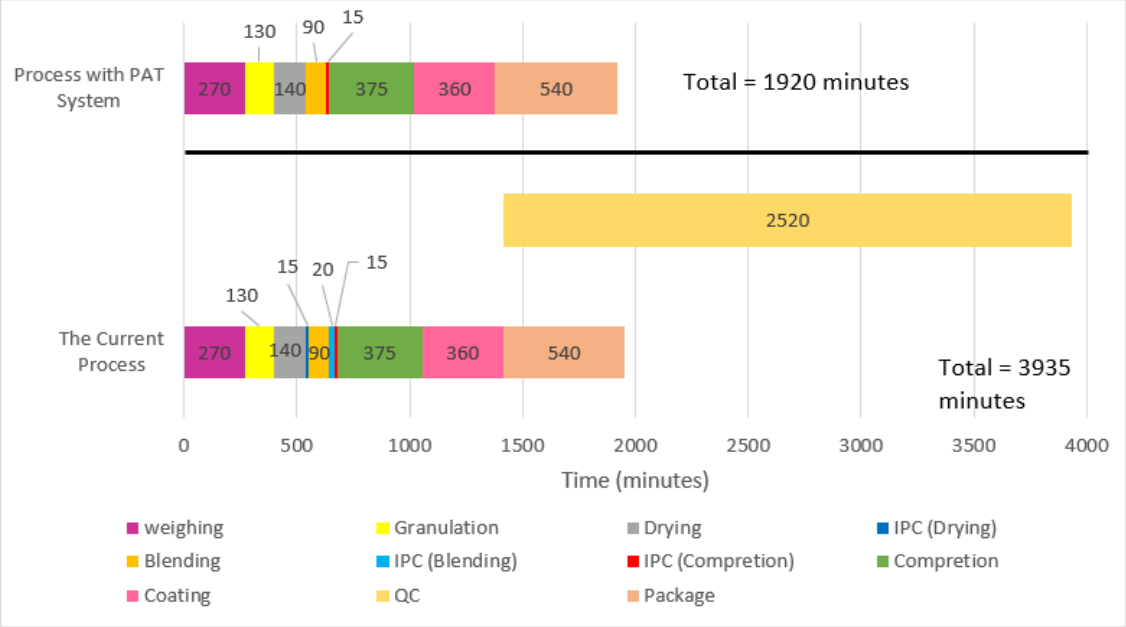

Figure 23: Comparison of the process time line with and without implementation of PAT for the manufacturing of Product X.

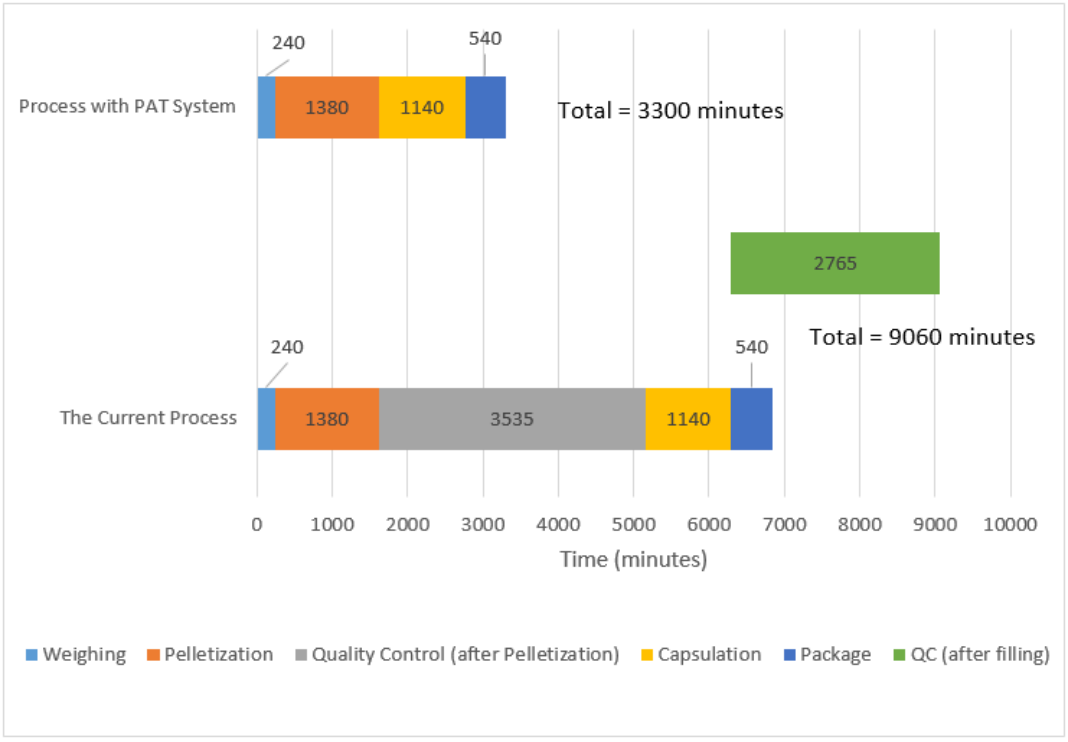

Figure 24: Comparison of the process time line with and without implementation of PAT for the manufacturing of Product Y.

An analysis of the number of Product X and Product Y (pellets and capsules) batches produced during the year of 2015 was performed (Table 30).

Table 30: Batches of Product X and Product Y produced in 2015.

Product		**Number of batches**
Product X	Coated tablets	37
Product Y	Pellets	11
	Capsules	34

There are no records of any problems occurred during the production of Product X and Product Y from 2010 to 2015, except in 2011 when two cases of alteration in the flavor of Product X and change in color of the Product Y were reported. After investigation of these problems, results did not confirm changes in flavor. Regarding the color change observed in omeprazole pellets, the reason was found to be a deficient the product storage. Others reclamations reported are presented in Table 31, most related with packaging.

Table 31: Reclamation reports of Product X and Product Y from 2010 to 2015.

Year	**Product X**	**Product Y**
2010	Tablets loss	-
2011	Tablets loss	Lack of one blister
	Flavor alteration	Change in the,color of pellets
2012	-	Alveolus empty
2013	-	Without print of expiration date and batch number
		Change in the pellets color
2014	Tablet cracked	Empty box
2015	-	Capsules loss

5.1.2 Analysis of quality control cost and time

The following section summarizes for both products, the costs associated with quality control and time occupation of all batches. The year of 2015 was considered as reference. For quality control of Product Y, two points over the process are used for samples collection. These samples are send to the quality control department. These process stages are located after the pelletization process (hereby called Product Y pellets control) and after the filling process (hereby called quality control of Product Y capsules).

5.1.2.1 Time occupation of quality control

Considering Product X (Table 32), related substances test is the most consuming step in terms of time. If a switch to a real time release, it is possible to save approximately 64 days each year. Need to be taken in attention that these times correspond to occupation of equipment and operators. The same analysis principle will be applied to all products from now on.

Considering the Product X situation, and as for Product Y pellets control (Table 33), the related substances test is the most time consuming step alongside with the residuals solvents test. If a PAT tool is applied to replace this situation, it has the potential to save approximately 27 days a year.

Table 32: Occupation time related with QC tasks for Product X.

Method	Equipment time (hours)	Analyst time (hours)	One batch		All batches	
			Total time (hours)	Total time (minutes)	Total time (hours)	Total time (minutes)
Assay	4	3	7	420	259	15 540
Identification of colorants and preservatives	6	-	6	360	222	13 320
Dissolution	5	4	9	540	333	13320
Related substances	18	2	20	1 200	740	44 400
Total	-	-	22	2 520	1 554	93 240

Table 33: Occupation time related with QC tasks of Product Y pellets

Method	Equipment time (hours)	Analyst time (hours)	**One batch**		**All batches**	
			Total time (hours)	Total time (minutes)	Total time (hours)	Total time (minutes)
Assay	4	3	7	420	77	4 620
Appearance	-	0.08	0.08	5	1	55
Particle size	0.33	-	0.33	20	4	220
Moisture	-	-	0.5	30	5.5	330
Dissolution	4	4	8	480	88	5 280
Gastro resistance	5	4	9	540	99	5 940
Related substances	18	2	20	1 200	220	13 200
Residuals solvents	10	4	14	840	154	9 240
Total	-	-	59	3 535	648	38 885

Finally, for QC of Product Y capsules (Table 34), the related substances test is as well the most time consuming step alongside with the residuals solvents test. For this case, the dissolution and gastro-resistance tests are not made because they are imported from certificated analysis of Product Y pellets. The microbiology test was not included in this analysis because it is only made every ten batches and requires only the analysis of one batch in a year. Implementation of real time release testing to all batches, it will save approximately 46 days a year.

Table 34: Occupation time related with QC tasks for Product Y capsules.

Method	Equipment time (hours)	Analyst time (hours)	One batch		All batches	
			Total time (hours)	Total time (minutes)	Total time (hours)	Total time (minutes)
Assay	4	3	7	420	238	14 280
Aspect	-	0.08	0.08	5	2.83	170
Dissolution	-	-	-	-	-	-
Gastro resistance	-	-	-	-	-	-
Related substances	18	2	20	1 200	680	40 800
Residuals solvents	10	4	14	840	476	28560
Uniformity of content	3	2	5	300	170	10 200
Total	-	-	34	2 765	1 567	94 010

5.1.2.2 Quality control costs

This section explores the costs associated with quality control considering the batches of Product Y (pellets and capsules) and Product X over the period of one year (year 2015 considered as reference). For the estimation of the costs, the next points were assumed:

- Reagents and HPLC columns were priced according to 2015 reference prices.
- Analysts time and analyses refer to the data presented in Section4.1.2.1
- Cost hour of analyst is calculated considering a net salary of 800 per month

Product X

HPLC columns, acetonitrile and impurities standards represent almost 100% of the quality control costs for Product X (Figures 25 to 27). Raw-material assay and identification of colorants and preservatives is not represented individually but only in the costs of all quality control tests for Product X, because we only considered the cost of analyst time spent to perform these analysis (Raw-material assay and identification of colorants and preservatives).

In the Figure 28 are represent the contribution of all tests for total cost of Product X quality control. It can be observe that all tests had almost the same contribution (around 23%) except a dissolution test only contributed 9%.

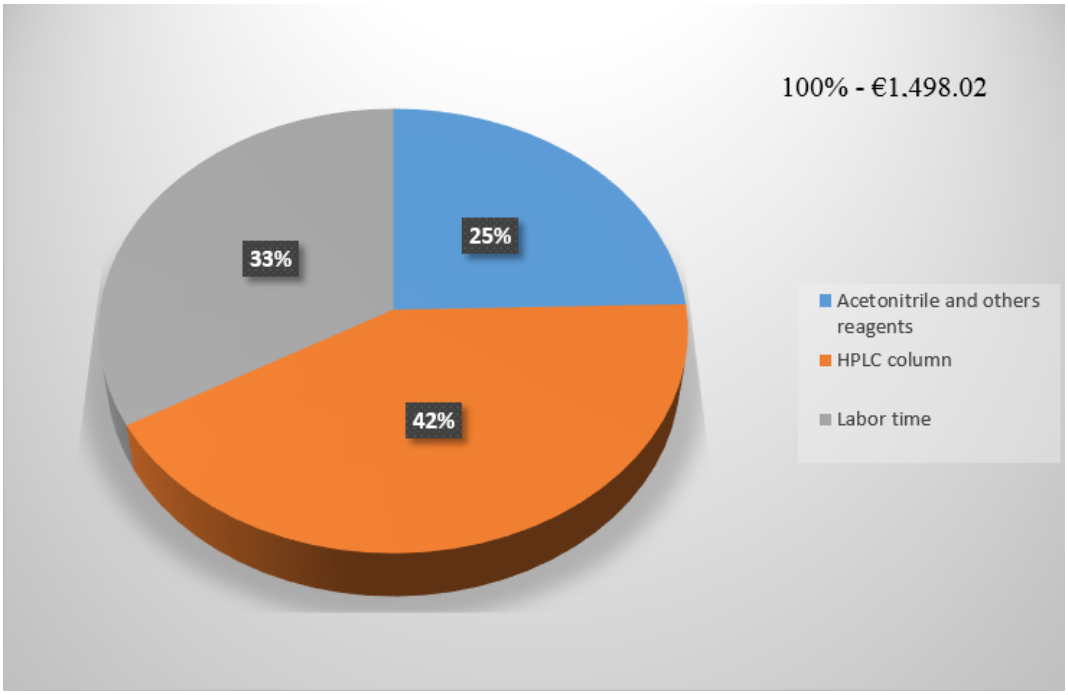

Figure 25: Assay test cost structure for Product X.

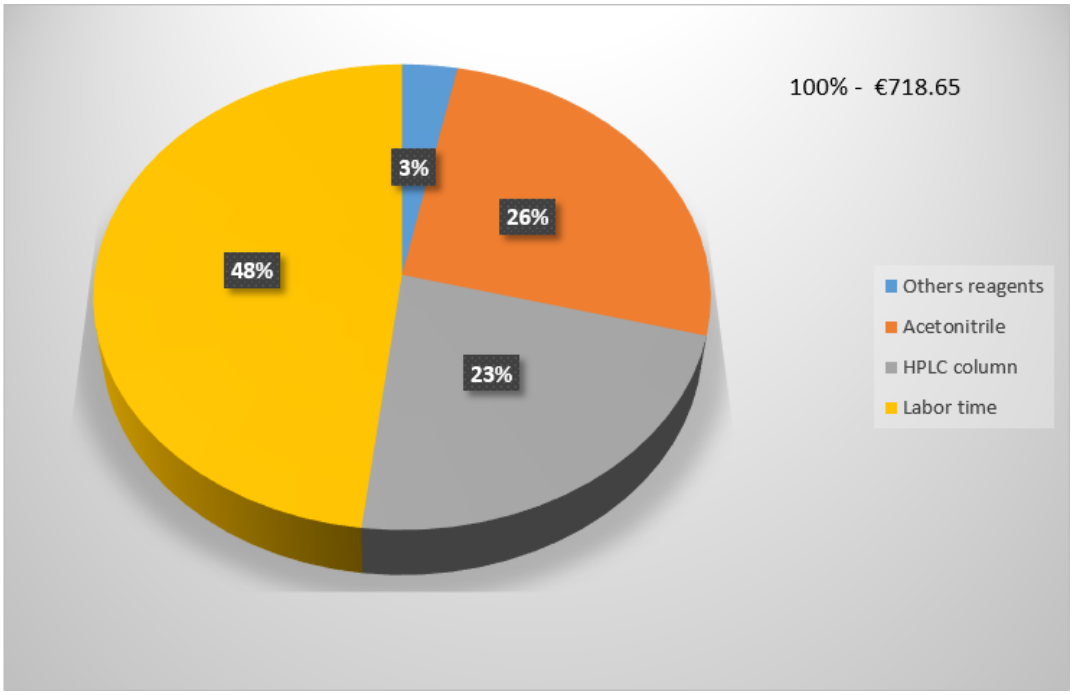

Figure 26: Dissolution test cost structure for Product X.

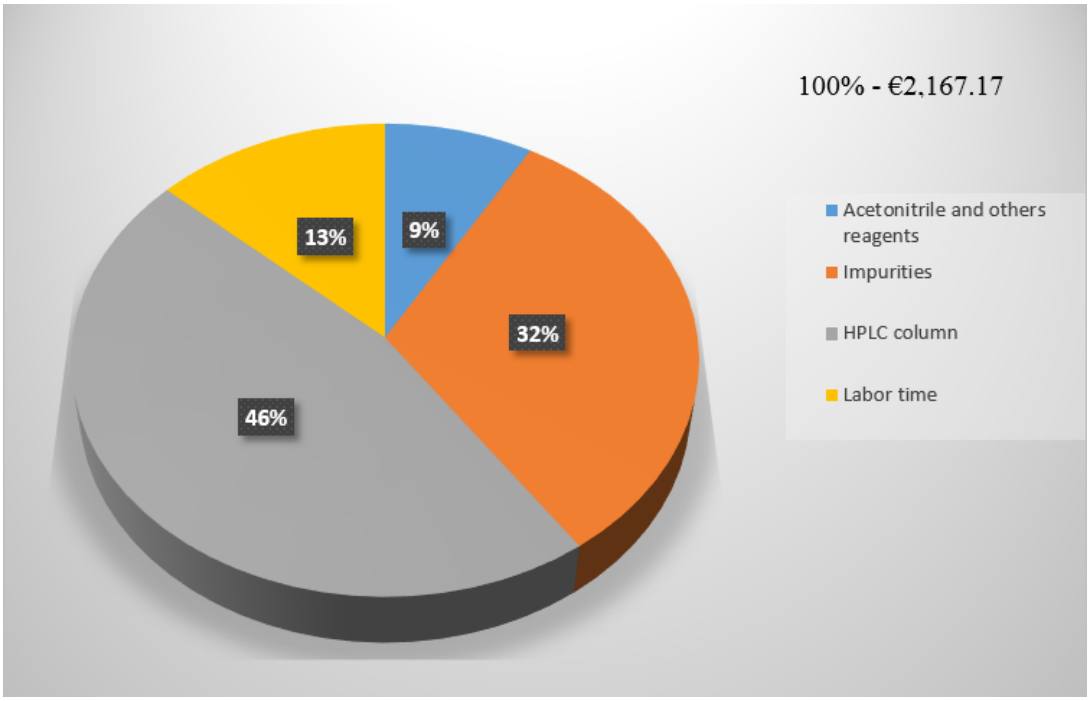

Figure 27: Related Substances test cost structure for Product X.

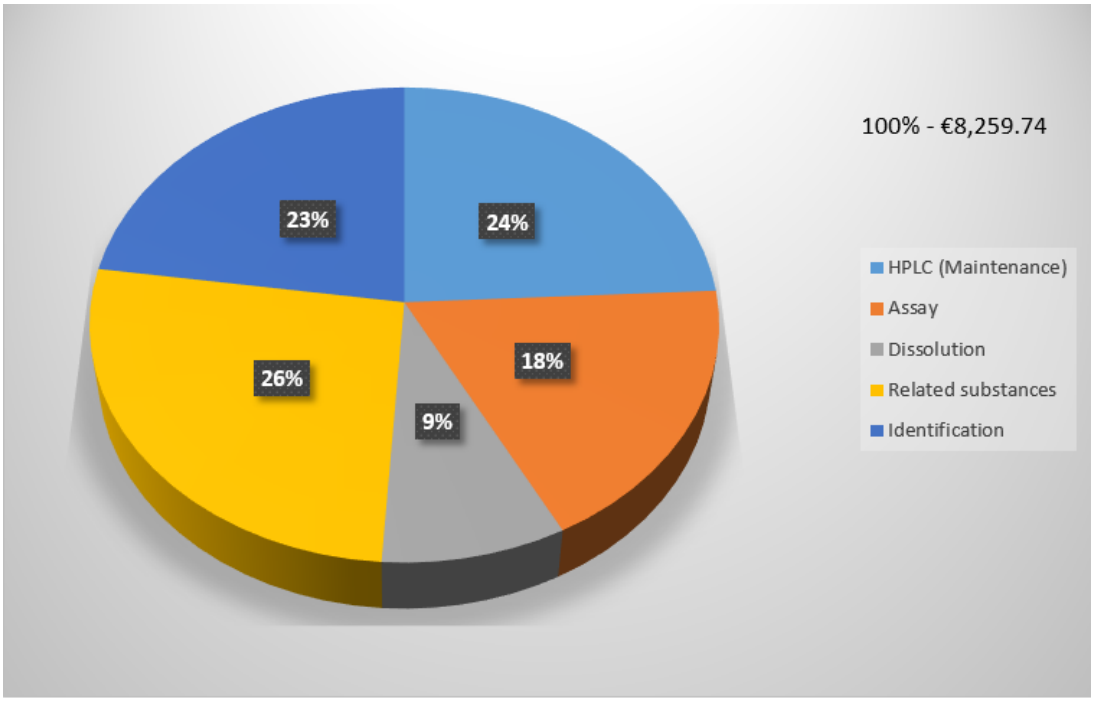

Figure 28: All QC tests cost structure for Product X.

Product Y

Like for the analysis of Product X QC, the HPLC column, acetonitrile and impurities standards represent the majority of quality control costs of Product Y pellets (Figure 29 to 33). The raw material assay test is not represented individually, because, like Product X, we only considered the cost of analyst time spent to perform this analysis (raw material assay).

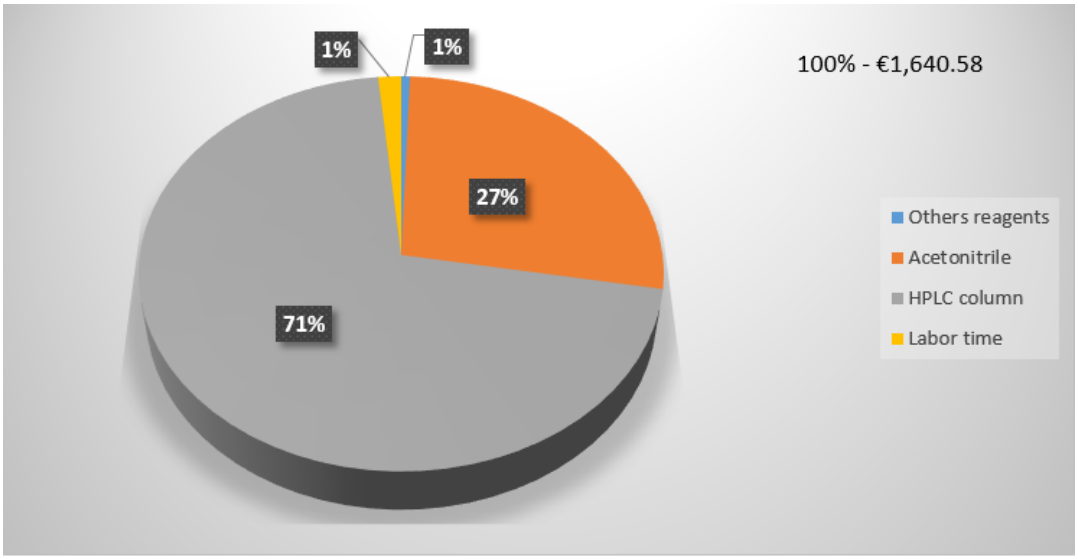

Figure 29: Assay test cost structure for Product Y pellets.

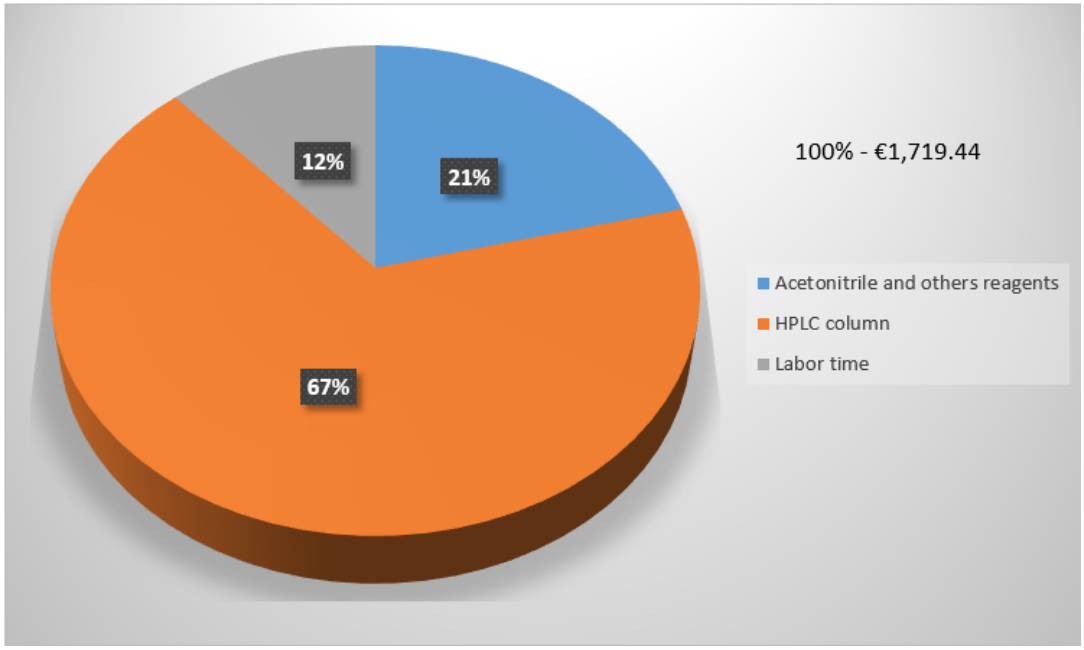

Figure 30: Gastro resistance test cost structure for Product Y pellets.

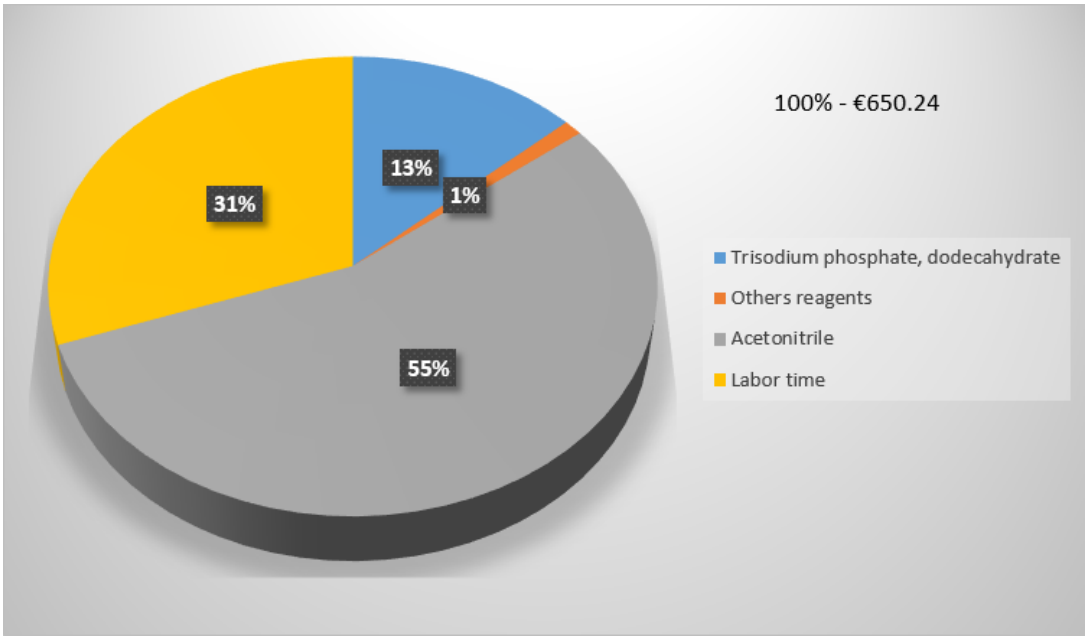

Figure 31: Dissolution (basic) test cost structure for Product Y pellets.

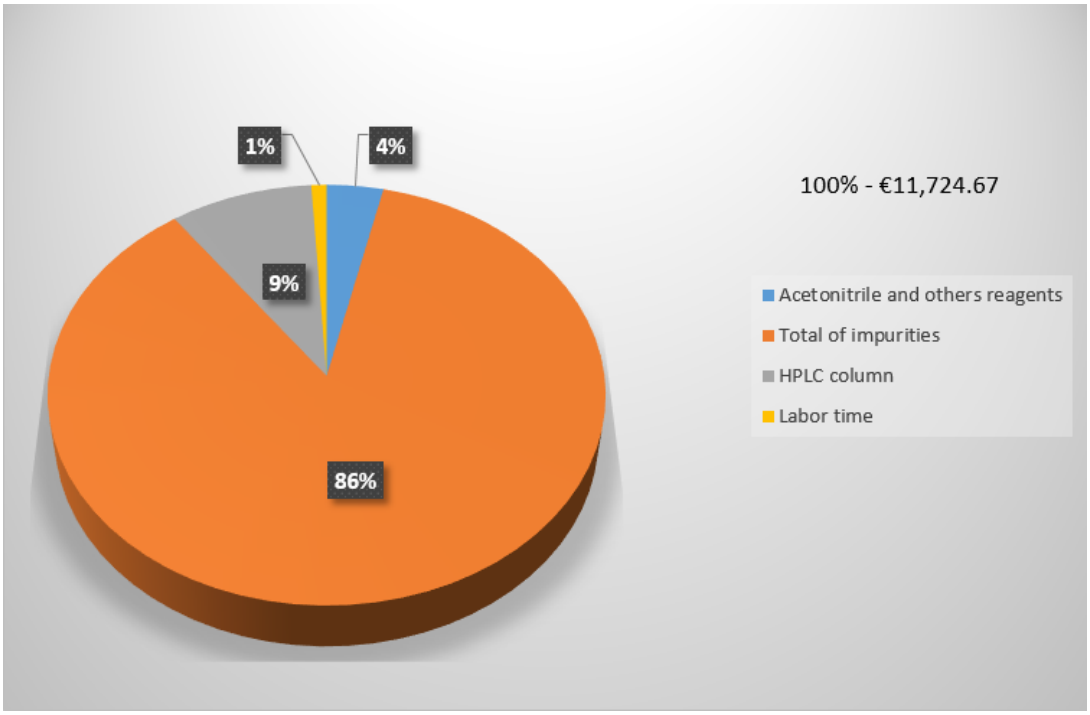

Figure 32: Related substances test cost structure for Product Y pellets.

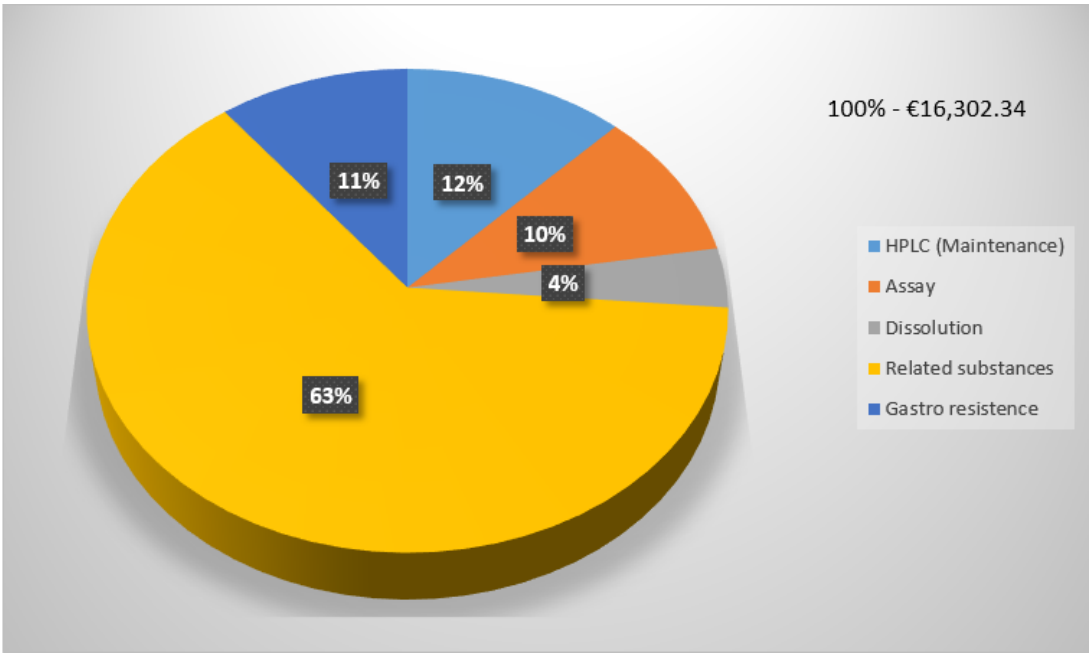

Figure 33: All Quality Control tests cost structure for Product Y pellets

In Figure 33, It can be observed that related substances testing represent a major cost (63%) and the dissolution test a minor cost (4%). Other tests (assay test, gastro resistance test and HPLC maintenance), have approximately the same contribution (around 11%).

From Figure 34 and 35 we represent the quality control cost for the release of Product Y capsules. In this case, we do not repeat the dissolution and gastro resistance tests because they are taken from the quality control report of Product Y pellets (Figure 30 and 31).

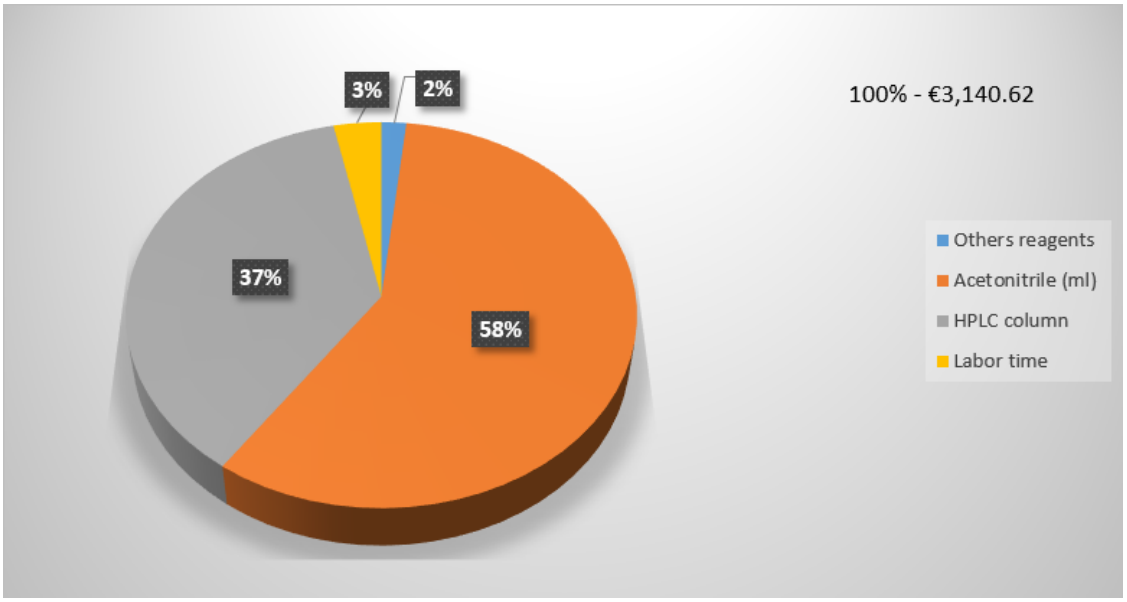

Figure 34: Assay test cost structure for Product Y capsules.

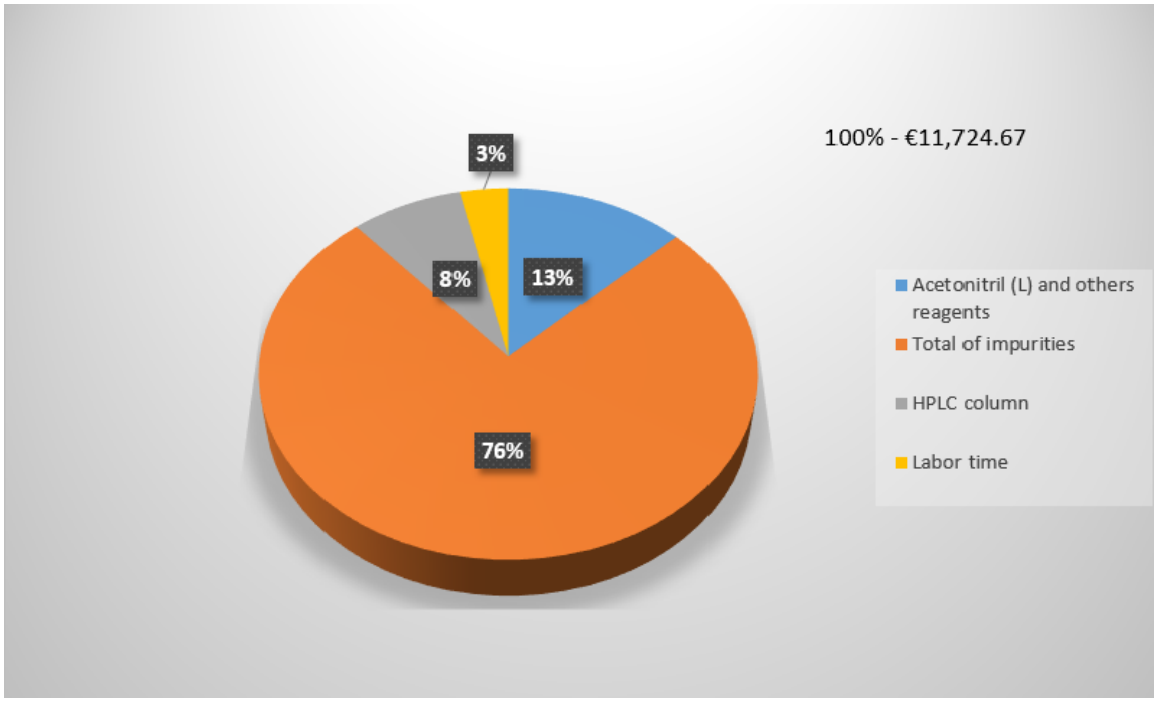

Figure 35: Related substances test cost structure for Product Y capsules.

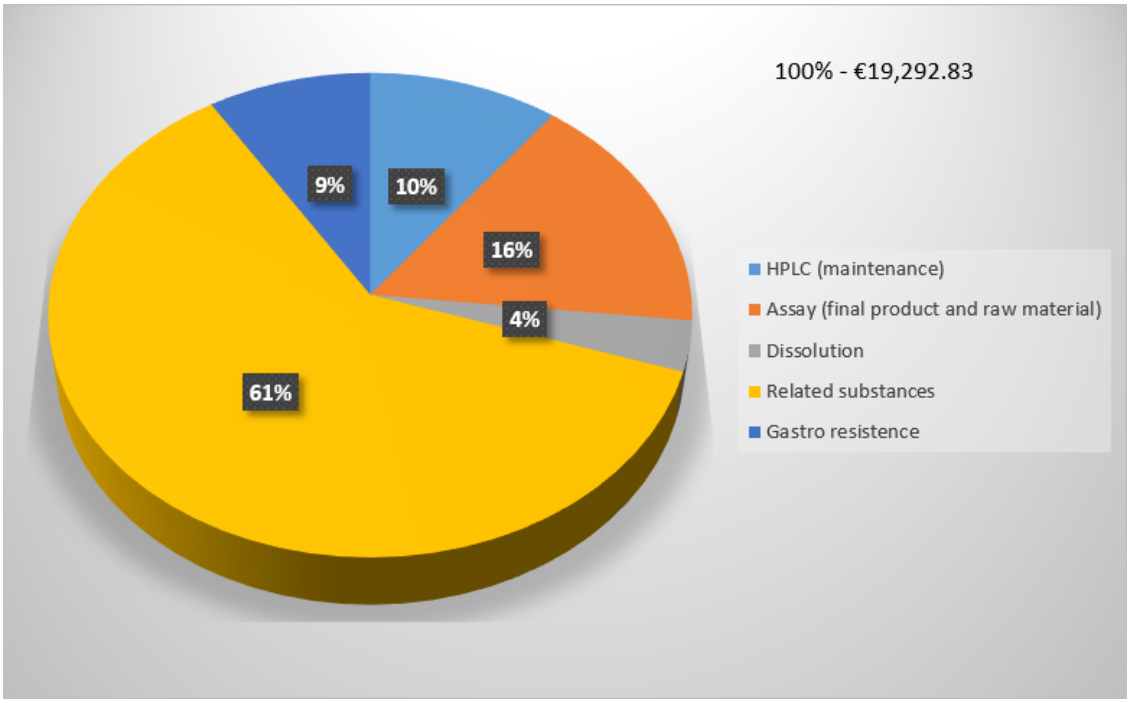

Figure 36: All QC tests cost structure for Product Y capsules.

It was verify in Figure 36 that the test most contribute for the total of quality control cost of Product Y capsules is the related substances test (61%). It can be also observe that assay test, HPLC maintenance and gastro resistance represent almost the equal weight in the quality control cost (16%, 9% and 10% respectively).

5.2 Equipment selection and cost

The production of Product X and Product Y was analyzed in Chapter 4. In there, we estimated the number of analytical instruments required for the implementation of PAT systems for these two products. Needed equipment is justified below:

- Quality control, development and investigation departments need one NIR spectrometer for the development of the models in case of impossibility of the use of equipment in the manufacturing area. Studies of new implementations on existing products or new ones can equally be done with this equipment. The Thermo Scientific Antaris II FT-NIR Analyzer with several modules (integration sphere, transmission and diffuse reflectance fiber optic) was selected. It gives the possibility of acquiring further accessories in the future to analyse other type of products, like creams, liquids, pastes or syrups.

- One NIR spectrometer Thermo Scientific Antaris MX FT-NIR Process Analyzer with two probes and respective fiber optics. One probes is required for the film coaters and another for the high shear granulator. This equipment offers the possibility to add two more probes and acquiring data from four sources simultaneously.

- One NIR spectrometer with wireless capability for the fluidized bed dryer/coater and bin blender. The VIAVI MicroNIR PAT W will be shared by these two pieces of equipment. Theres only the need to attach to the bin a MicroNIR PAT Standard Lid Mount Kit and for the fluidized bed dryer/coater a MicroNIR PAT Extended Probe Optic 10cm.

- One NIR spectrometer in the IPC department is required to analyze samples from all compression machines and capsule filling machines that are used to manufacture ibuprofen and omeprazole products, respectively. The Thermo Scientific Antaris II FT-NIR analyzer will require an integration sphere module and an auto sampling accessory for tablets and capsules.

Equipment vendors were contacted to determine budgetary cost estimates for the referred PAT equipment. The total equipment costs are listed in Tables 35 and represent a total of investment of €292,415.18

Table 35: PAT equipment costs for Product X and Product Y

Factory point	**Equipment type**	**Model**	**Modules/accessories**	**Price (€)**	**Reference**
Production line	NIR	Antaris MX Process	Main equipment	78,925.00	Thermo Scientific
			Optical fiber (with probe)	33,880.00	
	NIR	Antaris MDS II FT-NIR ANALYSER	Main equipment	37,653.00	Thermo Scientific
			Integration sphere	12,320.00	
			Auto sampler	19,250.00	
	NIR	MicroNIR PAT-W	Main equipment	38,279.26	Viavi
			MicroNIR PAT Standard Lid Mount Kit	3,627.42	
			MicroNIR PAT Extended Probe Optic 10cm	5,176.81	
			IQ/OQ/PQ Validation Documentation	4,373.60	
			IQ/OQ/PQ service & training	2,643.09	
Quality Control	NIR	Antaris MDS II FT-NIR ANALYSER	Main equipment	37,653.00	Thermo Scientific
			Integration sphere	12,320.00	
			Transmission	2,464.00	
			Optical fiber	3,850.00	
-	-	-	-	292,415.18	Total investment

5.2.1 Other costs

Table 36 contain other costs associated to this project. Methods development is calculated taking into account that a requirement of two analysts with a salary of €800 per month, working 22 day per month and 8 hour per day. Equipment maintenance is needed every 3 years, namely to change spectrometers light sources. This cost per instrument is estimated as €500.00 (essentially to change the light source). The dossier alteration of the products cost €2,000.00 per product. Finally, the cost for database (spectral libraries) and methods updating was considered. It is expected a need of 3 hours per week (assuming 52 weeks/year and a cost per hour of €4.55).

Table 36: Others costs associated to the project

Type	Products	Frequency	Cost(€)
Methods development and validation	All	yearly	9,600.00
Maintenance	All	every 3 years	2,000.00
Database and methods update	All	yearly	709.09
Dossier alteration	All	per product	2,000.00

5.3 Cost-benefit analysis

A preliminary analysis of costs and potential of time saving in terms of manufacturing of the selected products show that PAT has indeed ability to provide significant benefits in the reduction of the QC testing burden eventually leading to real time release. Since there is some uncertainty as to when real time release will be approved, two scenarios were evaluated for the economic analysis.

- The first scenario is the optimist case. It assumes that all equipment are installed, qualified and all process alterations approved within one year.
- The second scenario is a conservative case. It assumes that QC savings begin only in the third year.

In this chapter these two scenarios will be analyzed considering essentially the two analyzed cases. However, investment is not restricted to these two products and the PAT systems may naturally be used for other company products. Considering only the two products, investment is not profitable. The economic calculations will consider 15 products and assumes:

- the quality control cost of each product is the average between the Product X and Product Y since they represent roughly lower (Product X) and higher (Product Y) quality control costs;
- the development, the data base and model actualization cost is fifteen times more expensive because these costs rise when applied to more products and
- equipment maintenance cost is the same independently of how many products will be analyzed.

5.3.1 Calculations

Different formulas exist to estimate the benefits of installing new equipment in a manufacturing line. One of the methods and the simplest one is the earning before tax and interest calculation (EBIT). The EBIT for year i is calculated by adding the costs abolish with the project for each year, S_i, to the adding cost with the project in year i, Ci, and depreciation of the invest capital per year, DepI_C. The calculation of EBIT is represented in Eq. 1.

$$EBIT_i = S_i - C_i - Dep_{ic} \tag{1}$$

Eq. 2 includes the net cash flow for year i (CFi) Si represents the money saved by the investment in year i. Ci represents the maintenance and data base and model actualization cost.

$$CF_i = S_i - C_i \tag{2}$$

Another tool that can be used for estimating the return of investment is the net present value (NPV) of an investment represent in Eq. 3. This tool is based on the sum of cash flows. Unlike EBIT, NPV uses a discount rate (DR) to update the value of future cost, which takes into account the time value of the money and risk of futures cash flows.

$$NPV = \sum_{year=0}^{N} \frac{CF_i}{(1+DR)^{year}} \tag{3}$$

Another method of evaluation an economic benefit is internal rate of return (IRR). It's values are obtained when the discount rate would make the net present value of all cash flow equal to zero and it is describe by Eq. 4.

$$NPV = 0 = \sum_{year=0}^{N} \frac{CF_i}{(1+IRR)^{year}} \tag{4}$$

For the equipment investment, there is a required period of time before net profit is achieved. This is called the payback time. The payback time (Tpayback) is defined as the time needed for NPV is equals zero (Eq.5).

$$NPV = 0 = \sum_{year=0}^{T_{payback}} \frac{CF_i}{(1+DR)^{year}} \tag{5}$$

To simplify, it will be assumed that Tpayback is the first year of a positive NPV. At last, another tool used for evaluation of economic benefits is the return of investment (ROI). The calculation of ROI is made by adding of EBIT for years i of the project life time to the investment capital (IC) vesus the same IC and it is represent by the Eq.6.

$$ROI = \frac{EBIT_{\sum i} - IC}{IC} \tag{6}$$

These five formulas (EBIT, NPV, IRR, ROI and payback time) [25] were used to evaluate the cost savings of the investment described before. So to make these calculations possible, a series of assumptions and approximations were required.

Table 37: Resume of the expect benefits for post-PAT project

<table>
<tr><th>Not quantifiable benefits</th><th colspan="2">Quantifiable benefits</th></tr>
<tr><td rowspan="2">Stimulating internal
development and consolidation
of R&D department

Enhance the company image
for introduction of new technologies
on the production line

Increased confidence by
customers with introduction
of measures that reduce product variability
new subcontracting products
that use this type of control

Increment of new technology
that is support by regulatory
agencies (FDA, INFARMED and EMEA)</td><td>Quality Control</td><td>Reduction in 100% of quality control costs with application of real-time release.</td></tr>
<tr><td>IPC control</td><td>Reduction in 70% the IPC control costs</td></tr>
</table>

5.3.2 Summary of investment benefits

Table 37 describes the expected benefits for the post-PAT project.

Some of the benefits not included are:

- Reduction of costs associated with no quality batches. These costs include product reprocessing, tablet triage, batches out-of-specifications and variability.
- Reduction of required stocks. With the reduction of production time, it comes associated a reduction on the required stock of raw-materials and final products.

These savings are not accounted for cost/benefits of the project because this information do not exist or is not available at the moment.

5.3.3 Results

For both analyses scenarios (optimist and pessimist) a 15 year life for all of PAT equipment was estimated. In the case of the optimistic scenario, the PAT system is mounted and alteration of the document are approved within one year.

During the first year (optimist scenario) and first 3 years (pessimist scenario), it is assumed that are no cost benefits obtained by the PAT system. For the rest of the life-time of the project, there is a reduction or elimination of the QC expenses. Actually, the company uses a discount rate of 10% for these type of projects.

The total of the investment for all 15 products is €492,583.06, thats included the equipment (€292,415.18) and the methods development and validation (€144,000.00).

The benefits of the PAT system implementation with savings after one (optimist scenario) and three years (pessimist scenario) are given in Table 38.

Table 38: The benefits of the PAT system implementation after one (optimist scenario) and three years (pessimist scenario) for 15 products

	Optimist scenario	**Pessimist Scenario**
15 years NPV	€723,550.97	€451,307.57
IRR	33.2%	21.2%
Payback time (years)	5	8
ROI	363%	282%

The data show in both scenarios that the NPV is almost the double of the investment and the IRR more than the double of the discount rate. The payback time is lower than 8 years for both scenarios and the ROI is higher than 100%. With this information, the return of investment is acceptable and indicates that PAT implementation is economically feasible.

6 Conclusion

This work demonstrated, as is currently perceived by the pharmaceutical community, the importance and relevance of the integration of PAT tools in the manufacturing process of pharmaceuticals even considering the batch manufacturing mode. Regarding the two case-studies (products X and Y), this work showed that the presence of PAT tools in the granulation, blending and compression units (for product X) and pelletization and filling units (for product Y) is of up most importance.

In terms of Product X (coated tablets), PAT tools can identify in real-time the size of granules during the wet granulation process, the blending homogeneity during the blending process and dosage control during the tableting process ensuring a proper dissolution profile. For product Y it is important to apply PAT during the pellet coating process to evaluate the increase in the coating thickness.

Among the various identified PAT implementation opportunities for both products, the most attractive is the raw-materials control since there is no need of purchasing analytical equipment (already exist and can be expanded in terms of utilization). For production, the PAT solutions related with the monitoring of drying, blending and compression (product X) and pellet coating and capsule filling (product Y) were the most attractive since they might share the same analytical equipment making the initial investment less relevant. It should be noted that the optimal implementation of PAT equipment should consider mobility and adaptability given the high number of products manufactured by the company.

The presented PAT solutions are expected to be enough for a transition to RTRT, securing the control f the most relevant quality critical attributes in real-time, shortening the QC time needed, which is significative today in terms of total production time.

The economic analysis of the proposed technology implementation revealed that a total initial investment of €292,415.00 is required. It is natural that this investment cannot be returned considering exclusively the two products used as case-study. The extrapolation of the costs and benefits of this implementation for the remaining products in the company pipeline yielded (a total of 15 major products were considered) an estimation of NPV after 15 years of €749 679.00, in IRR=35.3%, payback in 5 years and a RoI of 399% considering in optimistic scenario. If a pessimistic scenario was adopted then in NPV after 15 years of €477 436.00 would be obtained together with a IRR=22.4%, payback-time in 8 years and a RoI=313%.

However, some barriers still exist in terms of adoption of this technology. Among these are the relatively high initial investment needed, a gradual change in the internal paradigm of quality control as well as integrating new ways of validating QC methods. The lack of qualified personnel that can cope with these barriers is often a justification for the non-investment in these Technologies. However, with the gradual integration of this subject in undergraduate and graduate courses, especially in pharmaceutical and engineering sciences will shortly overcome this problem.

Regarding the specific objective of this thesis it is proposed that in the future the following items should be explored:

- A detailed risk analysis for better understanding of PAT systems applied for the manufacturing of these products
- Evaluate with more detail other products that can benefit with this approach
- Explore the scientific and economic benefits of this technology in Research and Development departments.

In terms of PAT systems implementation in the pharmaceutical industry the following items should be explored:

- Use the PAT technology to facilitate the site transference of drug products.
- Reduce the burden related with development of PAT systems related calibrations.
- Increase internal knowledge in this area by the pharma companies.
- Encourage the continuous learning in this area of pharmaceutical industry collaborators (continuous professional training).
- Take advantage of PAT systems to start integrating continuous manufacturing processing replacing some batch manufacturing processes.
- Invest in the continuous research on new analytical devices with PAT capabilities and sampling strategies.

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