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Quality by design (QbD) and process analytical technology (PAT) applications in pharmaceutical industry

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ABSTRACT

Quality by Design (QbD) for the pharmaceutical industry includes the design, development and production control of products and production processes from the beginning to the end of the product development phase for ensuring the consistent quality of a pharmaceutical product. The QbD is a systematic scientific approach aimed at meeting the needs of the patient in the desired and targeted quality and aiming to produce the same quality pharmaceutical product in this direction. Process Analytical Technology, which is assessed in that regard, is part of a design quality approach that is used to design, analyze, and control real-time measurements of quality and performance criteria for raw and processed materials to achieve the desired final product. This scientific and systematic approach to pharmaceutical product development, which is also acknowledged and supported by the health authorities, serves to the changing and developing pharmaceutical sector.

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1. Introduction

The struggle of human beings while suffering from diseases, is a journey going on day by day from the existence and will continue as long as we exist. During this process, Doctors and Pharmacists are members of a professional group as old as human history, have used many different medicines based on plants, animals or minerals to be used in the treatment of diseases. The changing and developing world has brought evolution and globalization in the pharmaceutical sector. However, the only thing did not change is the importance of the drug quality. The pharmaceutical industry is a vital industry where product quality is vital and the ability to produce products constantly at the desired quality is indispensable [1].

The increasing world population causes changes on the welfare level of the societies, demographics, and living conditions, consequently the ecological equilibrium is affected. For this reason, health problems of people are also increasing. In this context, the quality of human life is directly parallel to the ability to produce the medicine in desired quality. Thus, the global pharmaceutical sector is constantly improving and investments in research and development (R&D) and innovation are increasing. The pharmaceutical industry is a lengthy and costly process involving clinical research where basic research and subsequent clinical tests are carried out, including the identification of effective molecules, the discovery of new areas of use for existing molecules, and the reassessment of a side effect for the drug under investigation [2]. Today, the development of new technologies to support R&D and production processes has brought along the development of quality medicines and new approaches in therapy. In particular, the computer-assisted experimental design is expected to reduce costs and increase quality in clinical research and manufacturing processes [2].

The American Food and Drug Administration (FDA) and the European Medicines Agency (EMA) make the definition of "Quality By Design" as a scientific, systematic, and risk-oriented approach to the production of pharmaceutical products from the empirical traditional processes [3]. This approach involves building the product by designing the stages of quality improvement, starting from the development of the pharmaceutical product. In addition, risks in the production phase are controlled by quality risk management. Guidelines such as ICH Q8, ICH Q9, ICH Q10, ICH Q11 and ICH Q12 published by the International Harmonization Commission (ICH) detail the scientific and innovative design and quality perception required to ensuring consistent product quality [3].

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Figure 1. Flow diagram for Quality by Design.

When the literature is examined, while there are a large number of studies [4-12] in which QbD and Process Analytical Technology (PAT) applications are analyzed, it is obvious that conducting more research in this area is necessary as the benefits of the field are taken into consideration. The approach of designing pharmaceutical products with quality rather than testing the final product during the pharmaceutical product development process, which is difficult and costly, is a topic that attracts growing interest. In this sense, the applications of the QbD and PAT in the pharmaceutical industry have been increasing. In this context, this study will present the advantages and disadvantages provided by PAT, PAT steps, PAT tools and PAT, by putting emphasis on the necessity of the QbD approach. Subsequently, the examples of the applications of PAT in the pharmaceutical industry will be summarized.

1.1. Quality by design steps

As shown in Figure 1, the first step in design and quality approach is to determine the intended use of the product and the appropriate quality addressing this purpose. In the second step, the scientific data and information necessary to define the critical quality characteristics are evaluated. In the next stage, process development is evaluated with concepts such as experimental design, process analytical technology and risk control. In addition, a design area ensuring quality in this step is established. The following step is the identification and design of the control strategy. In the last step, continuous improvement and life cycle are provided by the combination of quality risk management and product process knowledge.

In the traditional pharmaceutical development process, univariate experiments are reproducibility centered, while systematic experiments that are highly variable in design and quality are conducted in a design area and centered on the control strategy. However, in the traditional approach, the control strategy is predominantly composed of intermediate and finished product tests, whereas in the design approach the controls are made in the production phase and real-time release is the case. Additionally, process control is done with an off-line analysis in the traditional approach while PAT is used in design and quality understanding [1].

1.2. Proses analytical technology

The FDA (2004) defines process analytical technology as designing, analyzing and controlling the critical quality performance characteristics of the materials and processes in the process with real-time measurements to ensure the quality of the final product. The analytical term in this approach is generally referring to an integrated use with chemical, physical, microbiological, mathematical and risk analysis.

PAT's aim is to understand and control the production process that is consistent with our current drug quality system. In this respect, the quality concept for the pharmaceutical industry should be "The quality should be designed for pharmaceutical products and the products should be built in this direction, the quality tests applied to the final product do not show the actual quality" [13].

1.2.1. Proses analytical technology steps

PAT consists of three main steps in the form of the interrelated design, analysis and control (Figure 2). In determining the quality of the final product at the design step, it is necessary to determine the level of effects of each process step and starting material. In the analysis step, direct or indirect analytical tools are used in real time to determine the quality features of the process materials and raw material. Finally, in the last step, the harmony between all the results obtained through a process control is evaluated [14].

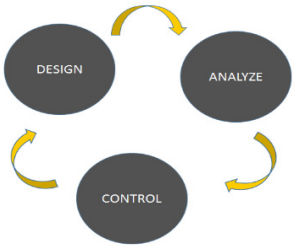

Figure 2. Process analytical technology steps.

1.2.2. Proses analytical technology tools

PAT tools include highly variable data acquisition, process analyzers, process control tools, and continuous improvement and information management tools for data collection and analysis. Raman Spectroscopy (RAMAN), Near Infrared Spectroscopy (NIRS), Ultraviolet-Visible Region Spectroscopy (UV-VIS) and Nuclear Magnetic Resonance Spectroscopy (NMR) are frequently used in PAT applications in the pharmaceutical industry. Particularly NIRS is widely used in the determination of process parameters and limit compliance, optimum values, and process termination points, in many units such as mixing, granulation, drying and coating during the production of the solid oral dosage forms.

On the other hand, on-line chromatographic methods and viscosity measurements are other important analytical tools used in the process development. In assessing the performance of the production process, chemometric methods, a useful tool for defining mathematical correlation, can be applied to real-time monitoring and control to realize the characterization of raw and intermediate products [1,14,15].

Table 1. Process analytical technology applications [a].

Application	PAT tool	Statistical chemometric method	Result	Reference
Wurster coating process	NIRS	PLS	Can be used for monitoring the Wurster coating process	[16]
To compare quality of pharmaceutical excipient	Raman spectroscopy [b]	PCA	The proposed approach can form the basis for a risk reduction management system	[17]
To optimize a tablet formulation	NIRS Raman spectroscopy	PCA	Tablet formulation can be designed by using QbD	[18]
To determine the quantification of active pharmaceutical ingredients using PAT	Fluorescence spectroscopy	PLS	Rapid and non-destructive method was developed simultaneous quantification of two active pharmaceutical ingredients in a tablet formulation	[19]
To develop a new method using direct analysis in real time mass spectrometry with PAT	DART-MS HPLC	Not required	Rapid process development method was proposed using PAT	[20]
To investigate on line quantitative monitoring of alcohol precipitation	NIRS	PSO, LS-SVM, PLS	Can be used as a process analyzer for noninvasive and online quantitative monitoring of alcohol precipitation	[21]
To investigate crystallization process	UV Vis [c]	PCA	PAT tools can be used to explore crystallization process	[22]
To evaluate and control the coating process of drug	NIRS	PLS	PAT can be used for drug coating process	[23]
Pharmaceutical granulation process	NIRS	PLS	NIRS is a useful PAT tool	[24]
Extraction process	NIRS	PLS	Successful models have been built and applied online for extraction process	[25]

[a] Abbreviations: NIRS: Near-Infrared Spectroscopy, PLS: Partial Least Squares, PCA: Principal Component Analysis, QbD: Quality by Design, DART-MS: Direct Analysis in Real Time Mass Spectrometry, HPLC: High Performance Liquid Chromatography, PSO: Particle Swarm Optimization LS-SVM: Least Square Support Vector Machines.
[b] Also, laser diffraction and X-ray powder diffraction methods were used.
[c] Ultra Violet/Visible spectroscopy, focused beam reflectance measurement (FBRM) and the CryPRINS software (Crystallization Process Informatics System).

1.2.3. Advantages and disadvantages of proses analytical technology applications

Perhaps the most important benefit of using the PAT to the pharmaceutical industry is that it can be intervened while the processes are going on. In other words, errors can be corrected while the process is in progress, so that material losses can be avoided. At the same time, since the real-time control strategy is concerned, the production efficiency can be achieved without sacrificing quality. In this respect, quality and stable products can be produced in a shorter period of time, in the context of better process control, providing long-term economic benefits.

One of the major problems encountered with PAT is the adaptation problem during the integration of the applications based on quality and design and PAT approach into the existing system. It is clear that revision of the traditional pharmaceutical product development process already in place needs a major role played by official authorities, applicants, and sectorial employees. This is because there is a need for training and working devotedly at every step to build this understanding based on quality building and to revise the existing traditional approach. Moreover, it is necessary to develop measurement tools and data analysis methods in order to better understand the chemical and pharmaceutical processes and to understand their contribution to quality.

2. Applications of proses analytical technology in drug industry as part of quality by design

PAT is used in different fields of the pharmaceutical industry such as extraction and crystallization processes, production of solid dosage forms, tablet pressing, quantification of active and auxiliary substances, blending, granulation, and coating processes. In this context, examples of different PAT applications used in the pharmaceutical industry are given in Table 1.

Naidu *et al.* [16] aimed improving understanding of multiparticulate drug delivery system by monitoring percent weight build-up during the functional coating process of drug-loaded pellets within QbD framework. An at-line NIR spectroscopy was used as PAT tool. The authors reported that they developed an at-line NIR spectroscopy method for monitoring the progress of Wurster coating operation without contacting and destructing the sample.

Hertrampf *et al.* [17] compared the quality of pharmaceutical excipients, manufactured on three different production lines. They aimed to identify which continuous process ensures a similar product quality to that of batch processing. For this purpose, different analytical methods were used. Authors reported that the proposed approach can form the basis for a risk reduction and management system with regard to sourcing and manufacturability.

Chavez *et al.* [18] studied to optimize the tablet formulation using QbD approach. For this purpose, Fourier Transform Infrared and Raman spectroscopy instruments were used as PAT tools. The authors analyzed the data by principal component analysis.

Warnecke *et al.* [19] aimed to determine the quantification of active pharmaceutical ingredients using process analytical technology. The samples were analyzed by Fluorescence spectroscopy and the data analysis was performed using a partial least squares regression. In addition, the goal of the study conducted by Yan *et al.* [20] was set to develop a new method using direct analysis in real time mass spectrometry as a PAT tool. Based on this PAT tool, the impacts of process parameters on the adsorption capacity were discovered rapidly. The authors reported that the proposed approach was model free and did not require use of any calibration model.

Jin *et al.* [21] aimed to use NIR spectroscopy for online and real time quantitative monitoring of alcohol precipitation. The developed NIR models were successfully applied for quantitative analysis of the critical intermediate quality attributes during alcohol precipitation. Simone *et al.* [22] designed their study to illustrate how an array PAT tool could be used at the crystallization process of a biopharmaceutical compound in the presence of impurities. The authors used different PAT tools to learn crystallization process of the biopharmaceutical compound.

Kim *et al.* [23] purposed to develop a validated NIRS method for evaluating and controlling the tablet coating process of a drug with low therapeutic dose, Glimepiride.

Rosas *et al.* [24] developed a method for the non-invasive determination of the critical quality attributes (CQAs) of a pharmaceutical granulate with a view to reduce its manufacturing time and to obtain a better knowledge of the effects of some variables used in the production process. They reported that near Infrared spectroscopy (NIRS) has been successfully used to develop faster and non-invasive quantitative methods for real-time prediction of the critical quality attributes (CQA) of pharmaceutical granulates (API content, pH, moisture, flowability, the angle of repose, and particle size).

Wu *et al.* [25] considered the feasibility of using NIR spectroscopy as a process analyzer for the non-invasive, online and real-time monitoring of extraction process for traditional Chinese medicine.

3. Conclusion

The quality by design for pharmaceutical products and processes is a systematic, scientific and risk-based approach to the development of every step involving in the pharmaceutical manufacturing in the direction of pre-determined goals. This approach controls the quality assurance of the drug, which is the biggest output of the pharmaceutical industry that has human health in the center. The process analytical technology that the design and the quality used together with analytical tools is a powerful quality by design used for designing, constructing, and controlling the quality of the product. It is known that the number of process analytical technology applications in the pharmaceutical industry are increasingly growing and hence, the number of license applications used this approach is rising rapidly. The understanding and implementing design and quality as well as process analytical technology practices increase the quality of pharmaceutical products, reduce costs over the long term, and modernize the supervision of the pharmaceutical industry. The continuity of drug quality is indispensable for manufacturers, supervisory agencies and patients, which makes these studies one of the priorities in the field and, requires further research.

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