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Process Analytical Techniques (PAT): A Review

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ABSTRACT

Process analytical technology (PAT) has been defined as a mechanism to design, analyze and control pharmaceutical manufacturing processes through measurement of critical process parameters which affect critical quality attributes. PAT checks the quality of raw material attributes both physically and chemically (i.e. at off-line, on-line, in-line). PAT involves a shift from testing the quality of building to the quality of products by testing at several intermediate steps. PAT saves a huge amount of time and money required for sampling and analysis of products. Pharmaceutical companies face many challenges and problems while implementing PAT into their new and pre-existing manufacturing processes. The potential for improved operational control and compliance resulting from continuous real time quality assurance was highlighted as a likely benefit that would result from PAT implementation. In this paper, we will start with brief PAT concepts, Introduction, PAT tools, Pat implementation and a review of their application in the wider pharmaceutical industry.

Keywords: Hyphenated techniques, NMR, High performance liquid chromatography, Critical Process parameters (CPP).

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INTRODUCTION

The term Process Analytical Technique(PAT) has been describe "a system for designing and controlling manufacturing through timely measurements (i.e. during processing) of critical quality and performance attributes for raw and in-process materials and also processes with the goal of ensuring final product quality into the product and manufacturing processes, as well as continuous process improvement.[1]

The concept actually aims at understanding the processes by defining their CPP's, and accordingly monitoring them in a timely manner (preferably in-line or on-line) and thus being more efficient in testing while at the same time reducing over-processing, enhancing consistency and minimizing rejects.

PAT allows for and encourages continuous process manufacturing improvement. It uses real-time information to reduce process variation and manufacturing capability and demands a solid understanding of the various processes involved in the operation. Simply put PAT is a real-time testing and adjustment based on the complete understanding of how the components and related processes affect the final product. This is in accordance with the fundamental principle that quality cannot be tested but is instead built into the medicinal product by design. [1]

The Food and Drug Administration (FDA) is inviting discussions throughout the pharmaceutical industry concerning a new mode of operation. Process analytical technology (PAT) is a key element of the Pharmaceutical Current Good Manufacturing Practices (CGMPs) for the 21st Century - a Risk Based Approach initiative announced by the FDA in August 2002 to improve and modernize pharmaceutical manufacturing. [4]

PAT is a system for

- Designing, analyzing and controlling manufacturing.
- Timely measurements.
- Critical quality and performance attributes.
- Raw and in-process materials. [1]

PAT goals

The goal of PAT is to design and develop dynamic manufacturing processes that can compensate for variability in both raw materials and equipment in order to consistently ensure a predefined quality at the end of the process. The central objective is to generate product quality information in real-time, in order for current and downstream operations to be adjusted accordingly. PAT aims to ensure that all sources of variability affecting a process are identified, explained and managed. [1]

Industry Driver

The growing use of more complex PAT within manufacturing industries is driven by increased technical capabilities providing better engineering controls. Historically, due to being such a highly regulated industry, the PAT initiative in the traditional pharmaceutical sector has lagged behind that of other industries.

With the more recent FDA directives, pharmaceutical companies have begun to change the framework in which they develop, implement, monitor, and control their manufacturing processes. Learning from other industries, pharmaceutical companies now realize that if a process can be monitored at critical points and the information used to actively control the process, then a consistent, reliable, lower-cost, and high quality final product results. Drivers to implement PAT include the opportunity for live feedback and process control, cycle time reduction and laboratory test replacement as well as risk mitigation. With such advances and knowledge of the product design space, there is the possibility of real-time-release as well as less scale-up and post-approval challenges for process or production site changes. PAT also carries the promise of new and innovative methods of production, as continuous monitoring allows for more controlled processes and better understanding and control of intermediate steps. [5]

How PAT Works

In order to successfully implement PAT, a combination of sequential steps is essential.

First, a unit operation or process must be defined as requiring PAT or being amenable to PAT deployment. In many cases, a thorough lab-scale feasibility evaluation of analytical methods is conducted to determine which techniques may have adequate sensitivity and selectivity. Additionally, PAT goes through extensive cost-benefit analysis as to which approach may reach the production floor.

Second, a suitable PAT technique needs to be chosen which would allow for measurement of the critical process parameter (CPP), preferably in an in-line or at-line manner. The first step away from off-line laboratory testing would be at-line testing, which moves process dedicated testing equipment to the production line. One approach of PAT is on-line testing, which draws samples and monitors periodically. Another mode is in-line testing, which places probes in constant contact with the drug product. The advantage of on- or in-line testing is better control because the analysis provides the most up-to-date snapshot of the process. [5]

Implementation of PAT

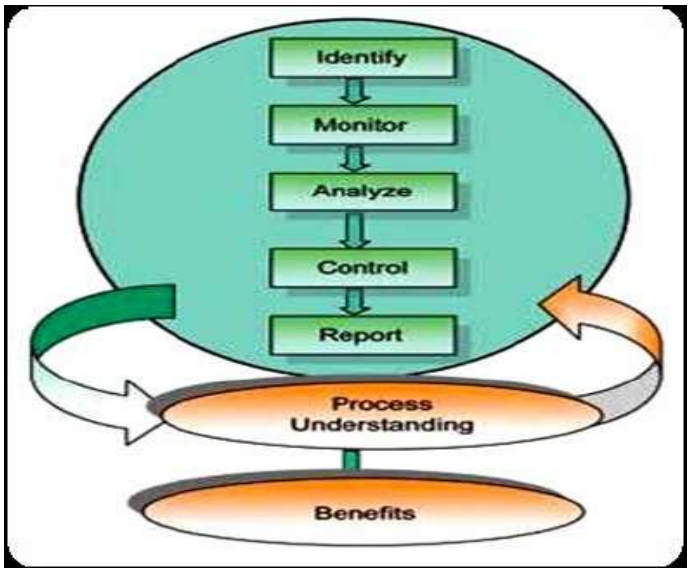

Figure 1: Proposed steps to PAT implementation [1]

Steps

Identify

This step includes the process of identifying an opportunity that would benefit from the PAT approach, as well as identifying the critical quality attributes that need to be monitored and controlled in the process.

Monitor

The next step after identifying the critical quality attributes would be to monitor them. Monitoring is usually achieved using on-line instruments. Recent advances in on-line analytical instrumentation have encouraged more online monitoring of parameters of interest. The simple premise is that we cannot control something we cannot monitor. The monitoring step allows us to collect data for the CQA of interest and evaluate the effect of adjusting the CQA on the overall process efficacy.

Analyze

The analysis step ensures that once we have identified our critical quality points and monitored them, we employ statistical analysis to determine how the critical quality attribute is related to the overall process efficacy. This step includes the development, verification, and validation of any statistical models that could define the process. Experimental studies, engineering test plans and retrospective analysis are methods that we are applied to analyze the CQA relationship to the overall process.

Control

After we have analyzed the relationship between the CQA and overall process efficacy and developed any statistical models, the next step in the PAT effort would be to control the process to ensure that the CQA is within specified limits at all times. This is the more critical step of the PAT roadmap that essentially ensures that "real-time quality assurance is meet.

Report

The reporting elements encompasses any tools that aid in assuring that the process was in fact in control throughout the processing period. Reporting tools serve two purposes-they allow for data to be reported in a fashion that aids in developing process understanding and that allow for any exception from the ideal state to be documented in final release report. [1]

PAT TOOLS

Analytical tools

The PAT document considers analysis as a method not just for the chemical analysis of a substance but for physical, microbiological, statistical, and risk analysis as well. Analytical pharmaceutical testing has traditionally occurred either off-line in a test laboratory or at-line in the production area. Off-line testing can result in a significant time lag between sample taking and results analysis. Similarly, at-line sampling can introduce physical artifacts and the potential for contamination. As a supplement to these methods, the PAT document recommends the use of other sampling methods.

These include:

- On-line methods, where sample is diverted from the main product stream and can be returned after measurement;
- In-line methods, where a probe (e.g. a pH electrode) is inserted into the process stream; and
- Noninvasive methods, where a sensor (e.g., a Raman detector) is used that never physically contacts the material, and the process stream remains undisturbed. [20]

Titrimetric techniques

In PAT there is application of titrimetric methods to (very) weak acids and bases as well as potentiometric end point detection improving the precision of the methods. With the development of functional group analysis procedures titrimetric methods have been shown to be beneficial in kinetic measurements which are in turn applied to establish reaction rates. There are many advantages associated with these methods which include saving time and labor, high precision and the fact that there is no need of using reference standards. [7]

2. CHROMATOGRAPHIC TECHNIQUES

Thin layer Chromatography (TLC)

Chromatography is the separation of two or more compounds or ions by the distribution two phases, one which is moving and the other which is stationary. These two phases can be solid-liquid, liquid-liquid or gas-liquid. Although there are many different variations of chromatography, the principles are essentially the same. The cellulose paper was the stationary or solid phase and the 1-propanol/water mixture was the mobile or liquid phase. This chapter explores a very similar micro scale technique for separating organic molecules, thin-layer chromatography. Thin-layer chromatography or TLC, is a solid-liquid form of chromatography where the stationary phase is normally a polar absorbent and the mobile phase can be a single solvent or combination of solvents. TLC is a quick, inexpensive micro scale technique that can be used to:

• Determine the number of components in a mixture

• Verify a substance's identity

• Monitor the progress of a reaction

• Determine appropriate conditions for column chromatography

• Analyze the fractions obtained from column chromatography [19]

High performance thin layer chromatography (HPTLC)

The HPTLC is very useful qualitative analysis method. Its combine arts of chromatography with quickness at moderate cost. Its major advance to TLC principle shorten time duration & better resolution. HPTLC is playing an important role in today analytical world, not in competition to HPLC but as complementary method. One of the most obvious orthogonal features of the two techniques is the primary use of reversed phases in HPLC versus unmodified silica gel in HPTLC, resulting in partition chromatography and adsorption chromatography respectively. Unlike other methods, HPTLC produces visible chromatograms complex information about the entire sample is available at a glance. Multiple samples are seen simultaneously, So that reference and test samples can be compared for identification. Similarities and differences are immediately apparent and with the help of the image comparison. Several chromatograms can be compared directly, even from different plates. In addition to the visible chromatograms, analog peak data are also available from the chromatogram. They can be evaluated either by the image based software Video scan or by scanning densitometry with TLC Scanner, measuring the absorption and/or fluorescence of the substances on the plate. TLC is an offline technique: the subsequent steps are relatively independent, allowing parallel treatment of multiple samples during chromatography. [9]

High-performance liquid chromatography (HPLC)

High-performance liquid chromatography (or High pressure liquid chromatography, HPLC) is a specific form of column chromatography generally used in biochemistry and analysis to separate,

identify, and quantify the active compounds. HPLC mainly utilizes a column that holds packing material (stationary phase), a pump that moves the mobile phase(s) through the column, and a detector that shows the retention times of the molecules. Retention time varies depending on the interactions between the stationary phase, the molecules being analyzed, and the solvent(s) used. The sample to be analyzed is introduced in small volume to the stream of mobile phase and is retarded by specific chemical or physical interactions with the stationary phase. The amount of retardation depends on the nature of the analyst and composition of both stationary and mobile phase. The time at which a specific analyst elutes (comes out of the end of the column) is called the retention time. Common solvents used include any miscible combinations of water or organic liquids. Separation has been done to vary the mobile phase composition during the analysis; this is known as gradient elution. The gradient separates the analyst mixtures as a function of the affinity of the analyst for the current mobile phase. The choice of solvents, additives and gradient depend on the nature of the stationary phase and the analyst. [12]

Gas chromatography

Moving ahead with another chromatographic technique, gas chromatography is a powerful separation technique for detection of volatile organic compounds. Combining separation and on-line detection allows accurate quantitative determination of complex mixtures, including traces of compounds down to parts per trillions in some specific cases. Gas liquid chromatography commands a substantial role in the analysis of pharmaceutical products. The creation of high-molecular mass products such as polypeptides, or thermally unstable antibiotics confines the scope of this technique. Its main constraint rests in the comparative non-volatility of the drug substances therefore, derivatization is virtually compulsory. Gas chromatography is also an important tool for analysis of impurities of pharmaceuticals. In recent years GC has been applied to estimate the process related impurities of the pharmaceuticals, residual solvents listed as impurity by the International Conference of Harmonization are analyzed by the GC using a variety of detectors. [7]

SPECTROSCOPIC TECHNIQUES

Spectrophotometry

Another important group of methods which find an important place in pharmacopoeias are spectrophotometric methods based on natural UV absorption and chemical reactions. Spectrophotometry is the quantitative measurement of the reflection or transmission properties of a material as a function of wavelength. [7]

Ultraviolet radiation having wavelengths less than 200 nm is difficult to handle, and is seldom used as a routine tool for structural analysis. The energies noted above are sufficient to promote or

excite a molecular electron to a higher energy orbital. Consequently, absorption spectroscopy carried out in this region is sometimes called "electronic spectroscopy". When sample molecules are exposed to light having an energy that matches a possible electronic transition within the molecule, some of the light energy will be absorbed as the electron is promoted to a higher energy orbital. An optical spectrometer records the wavelengths at which absorption occurs, together with the degree of absorption at each wavelength. The resulting spectrum is presented as a graph of absorbance (A) versus wavelength. Absorbance usually ranges from 0 (no absorption)
to 2 (99% absorption), and is precisely defined in context with spectrometer operation. Because the absorbance of a sample will be proportional to the number of absorbing molecules in the spectrometer light beam, it is necessary to correct the absorbance value for this and other operational factors if the spectra of different compounds are to be compared in a meaningful way. [8]

Raman Spectroscopy

Raman spectroscopy is suitable for quantitative analysis of pharmaceutical product because of the relationship between signal intensity and API concentration. Raman spectroscopy has been evaluated for identification and quantification of active ingredients in granulation, compression, drug pellet and both off-line and at-line. Raman spectroscopy has also been used to monitor hydration states of API. [7]

Near infrared spectroscopy (NIRS)

Near-infrared spectroscopy (NIRS) is a fast and non-destructive analytical method. Associated with chemo metrics, it becomes a powerful tool for the pharmaceutical industry. Indeed, NIRS is suitable for analysis of solid, liquid and biotechnological pharmaceutical forms. Moreover, NIRS can be implemented during pharmaceutical development, in production for process monitoring or in quality control laboratories. NIRS is generally chosen for its speed, its low cost and its non-destructive characteristic towards the analyzed sample. On one hand, the interest in NIR has increased thanks to the instrument improvements and the development of fiber optics that allow the delocalization of the measurements. On the other hand it has increased because of the computer progresses and the development of new mathematical methods allowing data treatment. While mid-IR spectra and especially the absorbance bands are directly interpretable due to chemical peak specificity, NIR spectra are difficult to interpret. [15]

Nuclear magnetic resonance spectroscopy (NMR)

NMR spectra have been a major tool for the study of both newly synthesized and natural products isolated from plants, bacteria etc. The introduction of reliable superconducting magnets combined with newly developed, highly sophisticated pulse techniques and the associated Fourier

transformation provided the chemist with a method suitable to determine the 3-dimensional structure of very large molecules. NMR spectroscopy has been mainly used for the elucidation and confirmation of structures. For the last decade, NMR methods have been introduced to quantitative analysis in order to determine the impurity profile of a drug, to characterize the composition of drug products, and to investigate metabolites of drugs in body fluids. For pharmaceutical technologists, solid state measurements can provide information about polymorphism of drug powders, conformation of drugs in tablets etc. Micro-imaging can be used to study the dissolution of tablets, and whole-body imaging is a powerful tool in clinical diagnostics. Taken together, this review will cover applications of NMR spectroscopy in drug analysis, in particular methods of international pharmacopoeia, pharmaceutics and pharmacokinetics. [18]

ELECTROPHORETIC METHODS

Capillary electrophoresis

Another important instrument essential for the analysis of pharmaceuticals is capillary electrophoresis (CE). Capillary electrophoresis in its different versions represents a powerful separation technique which proved sufficiently competitive /complementary to high performance liquid chromatography. Based on the simultaneous action of electro migration and electro osmotic flow this approach offers a wide range of conditions under which successful separations and quantitation can be obtained. While the ‘‘classical’’ version is limited to charged water soluble analysts only, who introduced micellar systems offered the possibility of separating uncharged analysts on the basis of their partition between a micellar phase and the aqueous background electrolyte. Consequently the potentials of this methodology have spread to all kinds of non-polar solutes. [17]

HYPHENATED TECHNIQUES

Chromatography - Produces pure or nearly pure fractions of chemical components in a Mixture and Spectroscopy Produces selective information for identification using standards or library spectra. “The coupling of a separation technique and an on-line spectroscopic detection technology will lead to hyphenated technique.” A Hyphenated technique is combination or coupling of two different analytical techniques with the help of proper interface hyphenated techniques ranges from the combination of separation-separation, separation-identification & identification- identification techniques. The term “hyphenation” was first adapted by Hirschfield in 1980 to describe a possible combination of two or more instrumental analytical methods in a single run. The aim of this coupling is obviously to obtain an information-rich detection for both identification and quantification compared to that with a single analytical technique. [13]

BENEFITS AND CHALLENGES OF PAT

Most industry representatives that either were involved in discussions regarding the feasibility of PAT. Positive perceived benefits of PAT include;

- Decrease in cycle times.
- Lower costs.
- Increased efficiency and batch-to-batch consistency.
- Process fingerprinting (signature) that would be useful for validation, scale-up, and confirming acceptable handling of changes.
- Increased process understanding and a decrease in variability, rejects, and lot failures.
- Possible continuous processing and the ability to adjust process on the basis of real-time monitoring data.
- Conversely, the most-common perceived or actual challenges include:
- Product-approval delays by inclusion of PAT methodologies into relatively traditional drug development and validation activities.
- Lack of a written PAT guidance document from FDA.
- increased pressures to meet aggressive filing timelines, added costs to make changes, lack of senior management support, and resource constraints. [25]

PAT APPLICATIONS IN THE PHARMACEUTICAL INDUSTRY

Innovations in the process analytical chemistry and in our ability to capture and analyze large amounts of data have served as the key drivers for adoption of PAT in the pharmaceutical industry. The key feature of PAT is that quality is built into the product, rather than being tested before release of product. The PAT framework comprises risk management, at/online sensors that assist in monitoring/controlling/designing of the process and prediction of process performance. A variety of analytical techniques have been used in the pharmaceutical industry, including Fourier transform infra-red spectroscopy (FTIR), UV-Vis spectroscopy, gas chromatography, high performance liquid chromatography (HPLC), X-ray diffraction spectroscopy, and NIR spectroscopy. [21]

PAT application at following sites

- RM Testing (warehouse based)
- Packaging Components
- Crystallization
- Blending (at- line or on- line)

- Drying
- Tableting
- Encapsulation (Coating thickness)
- Biopharmaceuticals
- Packaged product
- Equipment cleaning [21]

CONCLUSION

The use of Process Analytical Technology can provide huge benefit to the pharmaceutical industry by increasing product quality while delivering superior asset utilization and financial value. PAT provides better knowledge of raw materials by characterizing it both physically and chemically understanding of manufacturing parameters all which is having the impact on the finished product quality. This review is aimed at focusing the role of various analytical instruments in the assay of pharmaceuticals and giving a thorough literature survey of the instrumentation involved in pharmaceutical analysis.

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