REVIEW ON PROCESS ANALYTICAL TECHNIQUES AND IT’S TOOLS AND APPLICATION IN PHARMACEUTICAL INDUSTRY

Alka N. Chaudhary* and Kiran Singh

Department of Pharmaceutical Chemistry, School of Pharmaceutical Sciences, Shri Guru Ram Rai University, Dehradun-248001, India.

ABSTRACT

PAT is a system for designing, analyzing and controlling manufacturing processes by timely measurement of critical process parameters that affecting critical quality attributes. PAT monitors the quality of raw material properties both physically and chemically (i.e. at off-line, on-line, in-line). PAT requires a change from building quality testing to product quality testing in a variety of intermediate steps. It saves a large amount of time and resources required for sampling and review of products. The main objective of PAT is to provide effective tools such as multivariate data analysis and acquisition tools, modern process analyzers or analytical chemistry, controlling tools, endpoint process monitoring, and continuous improvement and knowledge improvement tools. Through this review, an attempt has been made to discuss the concept of PAT, benefits, different tools and applications.

KEYWORDS: Process Analytical Techniques, ICH, USFDA, QBD.

INTRODUCTION

Process Analytical Technology or PAT is a revolutionary tool in pharmaceutical industry given by the United States Food and Drug Administration (USFDA) to improve the quality of the product. The PAT understands and controls the manufacturing process, and is compatible with current drug quality system. The goal of this initiative is to build quality product and standardized manufacturing processes and to continuously improve the process. In 2001, PAT was launched by the Food and Drug Administration (FDA) to reduce the risk of
producing a poor or low quality product. With the help of PAT, pharmaceutical companies now are better equipped to build efficacious and design quality product. According to FDA Process Analytical Technology is defined as “a system for designing, analyzing and controlling manufacturing processes through timely measurement of critical quality and performance attributes of raw materials, in-process materials and processes with the goal of ensuring final product quality”. A regulatory framework for implementation of the PAT has been established by the FDA. Acc. to this framework “the FDA tries to motivate the pharmaceutical industry to improve the production process”. [1-5]

The fundamental principle of PAT is “quality is not tested, but it should be built into the product by design”. In order to achieve a high degree of repeatability and efficiency, active management of processes and quality assurance requires continuous and real time operation. [6] The idea is to understand the process by defining their critical process parameters and controlled in a specified manner (preferably in-line or on-line) and testing is more effective and over-processing is also reduced, thus increasing accuracy and reducing rejections. PAT continuously encourages process manufacturing improvement. [7-8]

![Fig. 1: Main areas covered by PAT.](image-url)
Concept

The efficiency of the traditional pharmaceutical product is assured and usually achieved by batch processing with final laboratory tests conducted on representative samples. Quality pharmaceuticals have been successfully delivered to the public by a conventional approach. Problem with this approach is that if final quality specification test is not passed by the product, then the entire batch will be discarded which followed by a massive loss to the company. Another problem is that if the quality specification is not met by particular representative sample but the overall batch is good, in this case whole batch will also be discarded on the basis of sample’s result. However, the problem is that if representative sample is passed and released on the basis of the results of the samples, but the overall batch is of low quality than the product will be recalled later from the market. So, FDA discusses a new mode of operation with the pharmaceutical industry, which will tackle with issues like these. This mode of operation is stated as Process Analytical Technology (PAT). Process Analytical Technology is a key component of the "Pharmaceutical Current Good Manufacturing Practices (cGMPs) for the 21st Century Risk-Based Approach" initiative announced by the FDA in August 2002 for improving and modernizing the pharmaceutical manufacturing. [9-10]

The PAT initiative was first proposed by USFDA and Centre for Drug Evaluation and Research (CDER) to improve health and cost compliance by applying modern process control and testing in the pharmaceutical industries.

In ICH Q8, Q9 and Q11 it is discussed that Quality-by-Design (QbD) is well-established in manufacturing and development of pharmaceutical drug product and substance. QbD gives an outcome which is a well-designed and understood quality product delivering the continuous performance. Knowledge gained during development helps in explanation of establishment of a design space, (process) control strategy and a point is set within the (regulatory approved) design space. An acceptable product is produced by materials which are made following design space, and the changes within the design space are (regulatory) acceptable. Analytical QbD (AQbD) have same concepts and principles that have been applied for development of analytical methods. Counterparts to process QbD, AQbD’s aim is to design a well-analyzed, robust method that consistently delivers necessary performance as told in analytical target profile (ATP). In-situ analytics, chemo metrics and modeling are sets of analytical tools used for pharmaceutical development and control, i.e., Process Analytical Technology tools. [11-15]
Benefits

Some uses of PAT tools which depends on the development or production phase are

- Helps in better understanding of chemical and physical mechanisms, the process safety is improved by detecting unstable intermediates; PAT tools are used for continued process understanding in the manufacturing plant thus helping to better investigate scale-up effects and improving the process.

- Helps in better understanding of processes.

- Batch-to-batch reproducibility.

- For improving process robustness and product quality.

- Batch rejection is prevented.

- Reduce the production cycle times.

- Cost is reduced, sampling and classical analyses is reduced (e.g. HPLC, GC and Karl-Fischer).

- Hygiene conditions are improved by avoiding sampling of highly active substances and reducing contamination by products and product modification.

- Increase the automation: To better control the processes and take decisions PAT tools are used. To serve this purpose, methods which are implemented should be validated and the equipment relating to process control system must be GMP compliant.

- Continuous processing is facilitated.

- Real-time release is enabled by PAT.\textsuperscript{[16-17]}

How pat works

The first step away from off-line testing is at-line testing. In order to achieve immediate results, it is necessary to move the dedicated testing equipment to the production line. We have an advantage of the elimination of transfer of samples involving time delay. Accelerated dissolution rate analysis, and near infrared (NIR) tablet analysis can also be included while excluding traditional tests like dissolution, assay, friability, hardness, and thickness. On-line testing is one approach of process analytical chemistry, either sampling or monitoring periodically and in-line testing is another mode, where probes are placed in regular contact with the drug product. Advantage of on/in-line is having complete control of the method. Near infrared (NIR) is one of the techniques that have achieved recent recognition as a means to add on or in-line analysis at the production level. Near-infrared light can penetrate into and through solid samples and do not destroys or reacts with samples. PAT is not limited to NIR
whereas NIR has gained most of the attention, many other monitoring forms are included, like Raman, Mid-IR, acoustic emission signals and other imaging techniques.\[18\]

**Fig. 2: How Pat works.**

**Development of pat**

Process/method/equipment validation, process controls following the standard operating procedure (SOPs), process instructions/master recipes, and off-line testing of samples in end of every batch are included in traditional quality systems of pharmaceutical industry. These types of system does not naturally encourage improvements in manufacturing processes. From several decades Process analytical chemistry (PAC) has been performed in the petrochemical industry. More recently, term process analytical technology has been used to describe this approach, utilizing analytical and process chemistry along with multivariate tools. PAT increases efficiency, and cost reducing tools are used to ensure that quality is built into the products while improving the understanding of processes. In 2002 a new initiative was announced by the Food and Drug Administration (FDA), Pharmaceutical Current Good Manufacturing Practices (cGMPs) for the 21st Century, to enhance and modernize the regulation of pharmaceutical manufacturing and product quality. From this initiative an idea of the early adoption of new technological advances was taken by the pharmaceutical industry. After cGMPs initiative more detailed PAT guidance was followed for the industry (FDA, 2004). Later on in the guidelines of the International Conference on Harmonization similar elements of risk analysis, real-time quality control and continuous improvement were also included.
Recently the latest initiative ICH Q10 ‘Quality Systems’ (5th June, 2008) which is the final stage of the harmonization process was achieved and then all parties to ICH (US, Europe, and Japan) concluded a scientific consensus on the guidelines through their individual regulatory bodies. Concepts behind ICH Q8 & pharmaceutical development is incorporates by ICH Q10.[19-22]

<table>
<thead>
<tr>
<th>Sr. no.</th>
<th>Laboratory measurement</th>
<th>Process analytical measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Complicated to use and requires a trained analytical chemist for operations</td>
<td>Automatic measurement</td>
</tr>
<tr>
<td>2.</td>
<td>Slow measurement</td>
<td>Rapid measurement</td>
</tr>
<tr>
<td>3.</td>
<td>Requires frequent maintenance</td>
<td>Doesn’t require frequent maintenance</td>
</tr>
<tr>
<td>4.</td>
<td>Samples may be pretreated prior to measurement to improved selectivity or sensitivity</td>
<td>Laboratory instrumentation are not subjected to harsh environments or corrosive samples.</td>
</tr>
<tr>
<td>5.</td>
<td>Laboratory instrumentation are not subjected to a harsh environments or corrosive samples.</td>
<td>Must be able to withstand the environment within chemical plant, followed by changes in temperature &amp; humidity.</td>
</tr>
</tbody>
</table>

Fig. 2 Difference between laboratory & PAT measurements.

Types of process measurement
- Off-line testing
- On-line testing
- At-line testing
- In-line testing

Off-line testing
Sample is transported from the chemical plant to a laboratory for measurement. Which is having the advantage of availability of sophisticated measurement system and trained laboratory personnel. But the transport and measurement are generally slow, requires hours to days thus yields historical data rather than data which is useful for immediate process adjustment. Hence off-line measurements are really quality control measurement i.e. these are useful in determination of certain specification of purity, quantity etc. of the product.

On-line testing
Either samples are drawn or monitored periodically. On line testing is used to keep check on the remaining water content during drying, by utilizing moisture sensors that calculates water vapor pressure, used for prediction of sublimation end point.
At-line testing
In this, the instrument is brought into the plant, which is more efficient, and still requires trained personnel. They are also subjected to the harsh environment of the plant, and still sufficiently rapid measurements may not be provided. Instrumentation requirements are different from those of laboratory instrumentation.

In-line testing
Drug product are placed directly in continual contact with the Probes. Better controlling of the process is an advantage of on/in line testing.[23-24]

Understanding PAT….!!
With Solid oral drug products
- For example, blend excipients and the drug substances till they are uniform and it is performed for individual tablet so that each is having consistent composition.
- In traditional approaches, blended samples are taken in many different positions in blender to confirm that the composition is formed homogeneously. Sometimes segregation within the sample may be caused by act of blend sampling itself thus resulting in analysis bias.
- In a PAT approach, a spectrophotometer will be attached to the blender and spectra are achieved in real-time and mixture is monitored. And when spectra does not changes any further, the blend is considered homogeneous.

Current blending process
- The CQA determined in laboratory are API content % homogeneity.
- Manual processing and analysis and laboratory implies a risk for human errors.
- PAT approach using that based on an NIR Spectroscopy, in-process assessment of CQA (API content and homogeneity) replaces manual sampling and laboratory analysis.
- Thus not only the human factor is removed, but CQA is acquired instantaneously during the manufacturing process.
- Technical issues should be resolved to get success in black implantation.
- Validation is also required.[25-26]

Pat tools
For generation of process understanding four PAT tools are needed as follows:
A. Multicomponent data accession and inspection tools

B. Procedure analyzers

C. Process observing and control tools

D. Knowledge management and Constant improvement tools

A. Multicomponent data accession and inspection tools: If see pharmaceutical products and processes from a physical, chemical, or biological perspective, they are complex multi-factorial systems. To identify optimal formulations and processes there are many development strategies that can be used. The foundation for product and process design is the knowledge acquired in these development programs, as follows:

- Recognition and evaluation of critical performance parameter.
- By recognizing failure modes and mechanism effects on product quality are quantified.

B. Procedure analyzers: Measurement collected (an-line, at-line, in-line) doesn’t need not be absolute values.

- Useful information for process control is provided by measurement of relative difference in material before and during processing.
- Firstly risk analysis must be done ensuring that this installation doesn’t adversely affects process or product quality than only process analyzers to be installed on existing process equipment in production.

C. Process monitoring and control tools: To ensure effective control of all critical quality attributes it is important to emphasize that there is a strong link between product design and process development. Procedure observation and control strategies observes the process’s state and to continue a desired state it is actively manipulated. The quality of input materials, the ability and efficiency of process analyzers to quantify critical attributes, and the achievement of process endpoints should be aligned with strategies so that stagnant quality of output materials and the final product is ensured. Following steps are included in design and optimization of drug formulations and manufacturing processes within the PAT framework (the sequence of steps can vary):

- Identification and measurement of critical material and process attributes are done in relation with product quality
- A process measurement system is designed which allows real time or near real time (e.g., on-, in-, or at-line) observing on all critical assets.
To ensure the control of all critical attributes which provide adjustment a process control is designed
- To grow mathematical relationships between product quality attributes and measurements of critical material and process attributes.
- For explaining acceptance criteria for end point attributes for reviewing measurement and sampling strategies rigorous statistical principles should be used.

D. Regular improvement and knowledge administrative tools: Combination of PAT large volume of water that are created changed into knowledge.
- Knowledge managing tools are used to store data to use models process simulation and process recognition tools which develop process knowledge and understanding.
- Information summarize electronic batch record external repository centralizers that and process instructions.
- Quality Assurance can verify the data.
- Computerized controls that can be built into electronic batch record that confirms quality is maintained and the risk of product recalls is reduced.\textsuperscript{[27-29]}

Pat implementation
Sample is transported from chemical plant to laboratory for measurement. Which has the advantage of the availability of sophisticated measurement system and trained laboratory personnel. But the transport and measurement are generally slow, requires hours to days, yielding historical data.

Key difference between the current practices in pharmaceutical manufacturing and a PAT approach are
- Novel analytical technologies and processes are used.
- Multifactorial relationships are established between materials, process and environmental conditions, and analyzing the outcome of these relationships for process robustness and product quality in manufacturing areas.
- Use of knowledge management tools.

PAT implementation is having four main elements
1. Building a science-centered knowledge base, an overall analysis of the process at the first principle and at the mechanistic level.
2. Process monitoring and controlled determination of critical procedure parameters and critical quality assets and to produce the desired quality the process is adjusted by selection of measurement, analysis and control mechanisms.

3. PAT system’s Validation.

4. Regulatory strategies.\[30\]

1. Building a science-centered knowledge base, an overall analysis of the process at the first principle and at the mechanistic level. PAT guidance highlights the requirement to grow a deep understanding of the fundamental scientific principles behind pharmaceuticals manufacturing procedures to control the critical parameters for the procedure and product quality. Three main ways in which the knowledge base supplied by the PAT approach is valuable:

- Robust process and product design should be established.
- Providing continuous learning throughout the product life cycle.
- It helps and explains pliable regulatory paths for inventive new approaches. Design of experiments, and the arrest and estimation of analytical measurement data are essential parts of building the knowledge base.

Examples of sources of variation
- The chemical and physical attributes of the supplied materials are impacted by changes in raw material manufacturing processes by distributor.
- Time centered changes in manufacturing performance (e.g., between equipment maintenance events).
- Effects which are associated with organized variations to equipment/analyzer, hardware and software of the system.
- Individual working methods (i.e., variations attributable to people in manufacturing sector).
- Modification of the local environment (e.g. temperature, humidity and other environmental conditions).
- Long term equipment using, ageing and degradation effects.

2. Process monitoring and control: Center for the design of the process monitoring, process control and QA strategies are analyzing the interaction between process and product and are utilized in manufacturing. PAT is a joint approach in which the process is controlled by the results obtained from the real time analysis of critical process control
points. During manufacturing process parameters are adjusted (within clearly defined limits) so that the desired product quality attributes are produce at the process end point. Nowadays in chemical and petrochemical industries are having the automation system that are required for this level of process control and are used extensively.[31]

Technologies used in PAT includes
Near infra-red (NIR), Raman spectroscopy, UV – visible Spectrophotometry, Fourier Transform Infrared (FTIR), X-ray Powder Diffraction (XRPD), Terahertz Pulse (TP) spectroscopy, NIR microscopy, Acoustic Resonance (AR) spectrometry, thermal effusivity, etc. Most popular and widely used technique is NIR spectroscopy.[32-33]

3. Validation of PAT system: The validation plan for PAT system typically includes the validation of software packages for data analysis, process analyzer hardware and software, process control software, IT systems for the management, storage and backup of results.[34]

4. Regulatory strategies: Establishment of a PAT policy development team of four subject matter experts was done which works with industries to ease discussion on proposed pat approaches at initial stages and to support the science and risk-based approach of the FDA to PAT.

PAT is a joint initiative of the Center for Drug Evaluation and Research (CDER), the Office of Regulatory Affairs (ORA) and the Center for Veterinary Medicine (CVM) in the context of the ‘cGMPs’. [35]

Pat applications in the pharmaceutical industry
Innovations in the process analytical chemistry (process analyzers) and our ability to capture and understand large amounts of data are the key drivers for adoption of PAT in the pharmaceutical industry. The key feature of PAT is too build quality products, rather than testing before releasing the product. Risk management, at/online sensors are present in PAT framework that assist in monitoring/ controlling/designing of the procedure and prediction of procedure performance. Varieties of analytical techniques that are used in pharmaceutical industry, includes Fourier transform infra-red spectroscopy (FTIR), UV spectroscopy, gas chromatography, high performance liquid chromatography (HPLC), X-ray diffraction spectroscopy, and NIR spectroscopy.[36-37]
Examples of PAT applications in the pharmaceutical industry.

<table>
<thead>
<tr>
<th>Application</th>
<th>Process analyzer</th>
<th>Statistical tool</th>
<th>Observation</th>
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<tbody>
<tr>
<td>Quick, precise and continuous tablet identification</td>
<td>Acoustic resonance spectroscopy</td>
<td>Principle components analysis (PCA)</td>
<td>A quick and non-corrosive process for on-line analysis and label comparison before shipping which helps to avoid mislabeling of drug.</td>
</tr>
<tr>
<td>For low-dose tablets content uniformity evaluated</td>
<td>NIR</td>
<td>PCA</td>
<td>NIR/PCA was used for prediction of uniformity of content of low-dose tablets manufactured by a direct compression process.</td>
</tr>
<tr>
<td>Monitoring capsule manufacturing at small-scale level</td>
<td>NIR</td>
<td>Partial least squares analysis (PLS)</td>
<td>PAT was utilized for testing of identity and quality of raw materials, for blend uniformity analysis, and for final content analysis of busulfan pediatric capsules.</td>
</tr>
<tr>
<td>Determining the mechanical properties of tablet containing drug</td>
<td>Air-coupled excitation and laser interferometric detection</td>
<td>Iterative computational technique</td>
<td>A non-destructive technique for physical characterization of the tablet is being provided after the inspection of vibrational resonance frequencies which is directly correlated with the mechanical properties of the tablet.</td>
</tr>
<tr>
<td>Terahertz pulsed imaging (TPI) used for examination of extended-release tablet film coatings</td>
<td>Terahertz pulsed spectroscopy (TPS)</td>
<td>-</td>
<td>Determination of tablet coating thickness, coating reproducibility, Distribution, and uniformity can be done easily. This method was validated against optical microscopy imaging.</td>
</tr>
<tr>
<td>NIR measurement of the potency of an API</td>
<td>NIR</td>
<td>PLS</td>
<td>Determination of potency of heparin active pharmaceutical ingredient was done with this non-destructive method.</td>
</tr>
<tr>
<td>Analysis of liquid formulations containing sodium chloride</td>
<td>Laser-induced breakdown spectroscopy (LIBS)</td>
<td>PLS</td>
<td>Less time-consuming method thus does not need any sample preparation.</td>
</tr>
<tr>
<td>Quantification of the active ingredient in pharmaceutical injectable formulations</td>
<td>NIR and UV-visible spectroscopy</td>
<td>PLS</td>
<td>More cost-efficient and beneficial and less time-consuming method for quantification of the lysine clonixinate.</td>
</tr>
<tr>
<td>Prediction of dissolution for a extended-release dosage form</td>
<td>NIR</td>
<td>PLS</td>
<td>For identification of differences in the composition of the coating polymers used for a tablet this method was used and thus assisting with prediction of dissolution behavior and process.</td>
</tr>
</tbody>
</table>

References:

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CONCLUSION
Using process analytical technology can bring huge benefits to the pharmaceutical industry by increasing product quality while providing superior asset utilization and financial value. PAT improves better knowledge of raw materials by characterizing both the physical and chemical understanding of the manufacturing parameters of all that has an impact on the quality of the finished product. Combining all these results together in a more robust process, a better product, a better process control and huge time saving which ultimately leads to a good savings, together with creation of a unique brand identity or image for the organization.

REFERENCES
30. Food and Drug Administration. General principles of software validation; final guidance for industry and FDA staff. Food and Drug Administration. 2002; 11.


