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Process Analytical Technology: A Review

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ABSTRACT

Process analytical technology (PAT) involves the use of different technologies and tools to build quality into the products. Effective PAT implementation comprise of science-based understanding of the physical, chemical and mechanical properties of all elements of the proposed drug product. The overall PAT venture is promising for delivering an integrated systems approach for quality design, process analysis, understanding and control, continuous improvement, knowledge and risk-based management. The incorporation of early PAT devices, increase process efficiency and safety by acting on data in real time and by eliminating sampling. PAT applications, increase detailed knowledge of processes, leading to increased robustness and greater processing opportunities. Modern developments in analytical technologies provide chemical and analytical insights for all types of chemical reactions and process monitoring such as drying, distillations, crystallizations, hydrogenations, and others.

KEYWORDS

Process Analytical Technology, ICHQ10, cost control.

INTRODUCTION

FDA defines Process Analytical Technology is 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. The Food and Drug Administration (FDA) launched PAT in 2001 to reduce the risk of making a poor product. With the help of PAT, pharmaceutical companies are now better equipped to increase process efficiencies and design quality product. With the goal of ensuring final product quality, it analyzes raw and in - process materials. PAT involves Measurement science by using conventional process sensors such as pressure, temperature and pH, Probes, as well as novel analyzer technologies. PAT focuses on the use of in-line testing using near infrared, Raman, or other the data retrieved would provide information on the properties of blends, cores, and other stages in the process. Through the use of probes in the process, uniformity, drying, and mixing endpoints, and other targeted stages can be pinpointed to a high degree of certainty. Sampling error would be minimized with in-line probes placed strategically throughout the production process. PAT is not a product or service. It is a concept, a working principle or a framework for operating, depending on you to implement it. The PAT market is developing and evolving rapidly as pharmaceutical companies strive to implement the framework set in place by regulators.[1] It uses real time information to reduce process variation and manufacturing capability. The PAT increases quality and reduces the number of costs in areas such as the chemical and pharmaceutical.[2]

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When to Introduce Process Analytical Technology (PAT):

Building quality into a pharmaceutical product has to be considered from the very beginning of the product's life. Essential preconditions are the equal involvement of and seamless communication between R & D and manufacturing. One purpose of PAT is bring quality into a product from the outset. It is thus essential for it to be involved in the R & D phase. If product Quality requirements are understood and implemented from the beginning root - cause analysis of quality or process failure after scale - up to commercial manufacturing will be much easier. This is why PAT could play an even more important role in the design and analysis of manufacturing processes, enabling performance control to be based on timely measurement of well - described critical processing data. Data processing needs should also be considered in the context of overall process Analysis strategy to meet emerging requirements for the speed and volume of data Collection. Real - time analysis supported by knowledge management requires collecting and gathering all production batch information, for example, by data warehousing. Thus, a PAT data management strategy based on online process analysis or data mining can be set up long before generating large sets of measurement data.

Historical data analysis should aim to cover method development, method validation and ongoing performance monitoring, as well as routine results for a given manufacturing process. Changing Current Practice Using PAT An approach integrating R & D and manufacturing will enhance process understanding and make acceptable risk management possible. A typical illustration of a PAT approach to quality improvement is the use of Near Infrared Spectroscopy (NIRS) to qualify excipients and active pharmaceutical ingredients just before they enter the production process, e.g.in dispensing. Near - infrared (NIR) spectra are informative about product structure and overall quality. Because with substances such as excipients the quality range was investigated at some time in the past and fixed into a calibration, NIR Measurement can provide simultaneous non-destructive confirmation of the predominant physical and chemical parameters. This is an effective method of reducing uncertainties about possible causes of failure or poor quality during production. Each time a given excipient fails its quality requirements at the moment of use, immediate action can be taken.[3]

Basis for Process Analytical Technology:

Despite the fact that the FDA's PAT framework began to take form just ahead of the creation of the twenty - first - century cGMPs initiative in 2001, it is well known that several of the core concepts were pioneered decades ago by other manufacturing industries such as fine chemicals, semiconductors, petroleum, and consumer products. The main concepts that differentiate PAT from the traditional industrial pharmacy skill set (including pharmaceutical and materials science, chemistry, and engineering) are process analytical chemistry (PAC) and advanced manufacturing science (Figure 1).

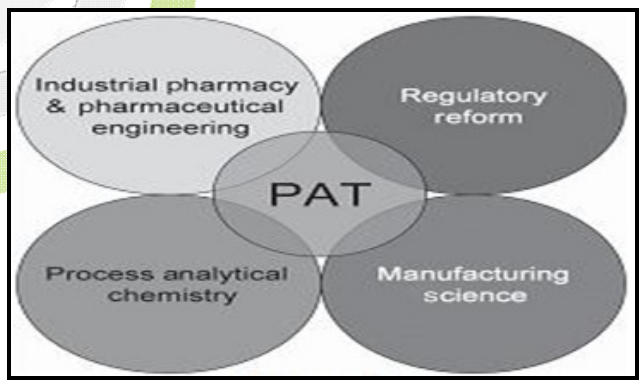

Figure: 1 PAT

Process analytical chemistry generally describes the science and technology associated with displacement of laboratory based measurements with sensors and instrumentation positioned closer to the site of operation. The goal of PAC is to "supply quantitative and qualitative information about a chemical process for monitoring, control, and optimization".[4] The more recently launched initiative "Quality by Design" (QbD) is also aligned with the PAT concepts.[5] Quality by Design has been defined

in the ICH Q8 guideline as "a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management".[6]

Development of PAT:

Traditional quality systems in the pharmaceutical industry include process/method/equipment validation, process controls according to standard operating procedures (SOPs), process instructions/master recipes, and off-line testing of samples at the end of each batch. This kind of system does not inherently encourage improvements in manufacturing processes. Process analytical chemistry (PAC) has been performed in the petrochemical industry for several decades. More recently, the term process analytical technology (PAT) has been used to describe this approach, which utilizes analytical and process chemistry along with multivariate tools. PAT tools are used to ensure that quality is built into the products while improving the understanding of processes, increasing efficiency, and decreasing costs. In 2002, the Food and Drug Administration (FDA) announced a new initiative, Pharmaceutical Current Good Manufacturing Practices (cGMPs) for the 21st Century, to enhance and modernize the regulation of pharmaceutical manufacturing and product quality. This initiative included an idea of the early adoption of new technological advances by the pharmaceutical industry. The cGMPs initiative was followed by more detailed PAT guidance for the industry (FDA, 2004). Similar elements of risk analysis, real-time quality control and continuous improvement were later included in the guidelines of the International Conference on Harmonization (ICH Q8, 2005; ICH Q9, 2005). The latest initiative ICH Q10 'Quality Systems' achieved recently (5th June, 2008) the final stage of the harmonization process. The outcome was that all parties to ICH (US, Europe, and Japan) reached a scientific consensus on the guideline's text and agreed to implement fully the guideline through their individual regulatory bodies. ICH Q10 incorporates the concepts behind ICHQ8 & 'Pharmaceutical Development.[7]

Table 1: Process Analysis Differ from Laboratory Measurement[8]

SR.NO	LABORATORY MEASURMENT	PROCESS ANALYTICAL MEASURMENT
1.	It is complicated to use and require trained analytical chemist for operations	It is a automatic measurement
2.	Slow measurement	Rapid measurement
3.	Requires frequent maintenance	Does not require frequent maintenance
4.	Samples may be pretreated prior to measurement to improved selectivity or sensitivity	Samples need not be pretreated prior to measurement
5.	Laboratory instrumentation is not subjected to a harsh environments or corrosive samples.	It must be able to withstand the environment of the Chemical plant, with change in temperature & humidity.

Types of Process Measurement:

1] Off-line testing

2] On-line testing

3] At-line testing

4] In-line testing

Off-Line Testing

Transport of sample from the chemical plant to a laboratory for measurement. It has the advantage of the availability of sophisticated measurement system and trained laboratory personnel. But the transport and measurement are generally slow, requiring hours to days, yielding historical data rather than data that can be used for immediate process adjustment. Hence Off-line measurements are really quality control measurement. i.e. they are used to determine whether the product meets certain specification of purity, quantity etc.[9]

On-Line Testing

This either draws samples or monitors periodically. On line testing used to monitoring of residual water content during drying, by use of moisture sensors that measure water vapor pressure, has been used to predict sublimation end point.[10]

At-Line Testing

In which the instrument is brought into the plant, are more efficient, but still require trained personnel. They are also subjected to the harsh environment to the plant, and still may not provide sufficiently rapid measurements. The instrumentation requirements will differ from those of laboratory instrumentation.

In-Line Testing

In which places probes in constant contact with drug product. The advantage of on/in line testing is better control of the process.[9]

Importance of PAT:

Cost control, by efficient production processes, and partly through the minimization of the necessity of final discard (or reprocessing) at the QA final test point, is an important justification for exploring PAT. In a world in which financial issues have entered a triage of decisions, cost control has become tightly entangled with patient treatment and cure, PAT brings other important advantages, however. Even the most rigorous military sampling of end product has a statistical chance of missing a problematic situation. In fact, in the most dangerous of circumstances – human blood processing, for example – regulation and practice call for testing of all end products rather than a representative sample. However, the addition of monitoring during production as well as at end stage, even if redundant, can only enhance the likelihood of catching aberrant situations and increasing patient safety PAT also carries the future promise of new methods of production. Continuous monitoring allows more controlled processes and a finer control of interim production steps. In vaccine production and protein separation technologies, the continuous monitoring of PAT could potentially enhance the speed and quality of end- product development.[11]

PAT Applications:[12]

1) Packaging Components. 2) Blending (at-line or on-line). 3) Drying. 4) Tableting. 5) Encapsulation. 6) Tablet Coating (coating thickness). 7) Packaged Product. 8) Particle size. 9) Content uniformity. 10) Contaminant Detection. 11) Pellet manufacturing.

Table 2 Benefits of Implementing PAT in the Pharmaceutical Industry[13]

Categories to be Benefited	PAT Benefit
Reduced operating cost	Increased operating efficiencies Improved cycle time Decreased operating costs Possible continuous processing Increased capacity utilization Attain production schedule Reduced reprocessing expenses
Quality Improvements	Increased quality (decreased product variability, decreased number of rejections, scrap, batch failure and systems failures; and increased product

	reliability) Increased regulatory compliance Increased product uniformity Increased process understanding Quality designed into the process
Positive regulatory impact	Moderate regulatory burden on FDA Improved scientific basis for regulatory functions
Minimize environmental impact	Reduced environmental impact Minimize waste generation during manufacturing

Examples of Application of Process Analytical Technology:

Particle Size

The particle sizes of active pharmaceutical ingredients (APIs) and excipients are of significant importance in most solid dosage products and are traditionally monitored by thief sampling followed by laboratory analysis. For systems where particle size is critical, this method of control suffers from several limitations. A small sample may not be representative of bulk product. Time is required to sample, transport, measure, and report results. There is possibility of exposure to operators and lab personnel. The cost of rejected lots can be high. All these limitations make traditional control methods impractical for real time quality assurance.PAT approaches to particle size measurement sample larger, more representative portions of bulk product and offer rapid analysis with immediate feedback directly into the control system. Because PAT is a closed system there is no exposure to personnel.[14]

Content Uniformity

A primary goal of blending is production of a uniform mixture of API and excipients in the final dosage form. Incomplete mixing is difficult to detect in the final dosage form because measurements of component identity and concentration are often not specific to distribution. Typically blend uniformity is assumed by blending for a set time and is actually monitored by release testing. This approach suffers from several limitations: Release testing on limited samples may not be representative of bulk. Blending for longer than necessary increases cycle time. Variations in feed materials may alter blend time from batch to batch. Excessive blending may lead to 'de-mixing. 'Failed release tests jeopardize the entire batch. A PAT approach to blending provides process understanding and feedback to more precisely control blending.

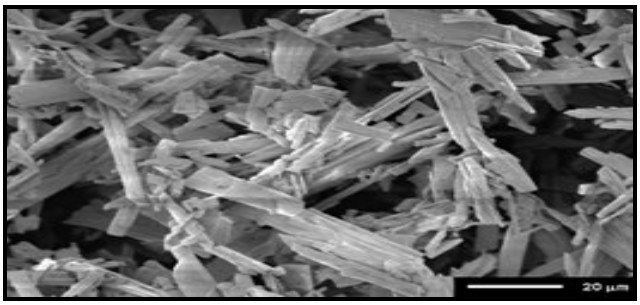

Figure 1: Without particle size control

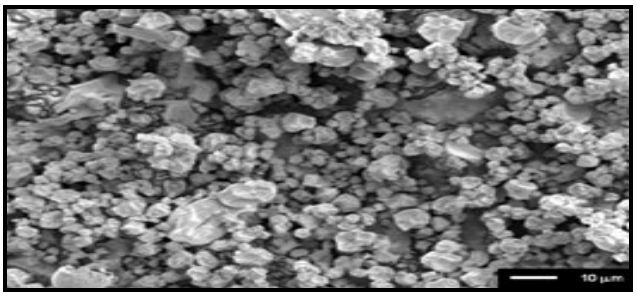

Figure 2: Tight particle size control

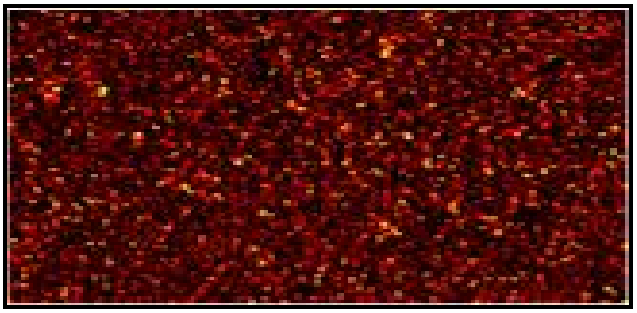

Figure 3: Blending carefully controlled

Figure 3 shows a Raman microspectroscopic map of a tablet surface where blending was carefully controlled. The uniform distribution of API (red and yellow dots) confirms that

blending was optimized for distribution. By measuring to an endpoint, blending could be discontinued when a desired distribution was reached, thereby minimizing cycle time. By careful selection of critical controls and measurement strategies, important properties of incoming materials could also be monitored to provide optimum conditions for blend uniformity.[15]

Drying

Product drying, either after synthesis or during processing, is a necessary step that can have a dramatic impact upon the solid form of the final product. A drying step may be designed to simply remove excess solvent for subsequent processing, or it may be an integral part of solid-state form manipulation through dehydration or desolvation. Under most scenarios, drying is carried out for a set amount of time, which can lead to excessive cycle time and/or undesirable form change if drying continues beyond the endpoint. Batch-to-batch variations in feed materials may cause uncompensated variations in drying time; failed release tests may jeopardize the entire batch.

A PAT approach provides the process understanding and measurement strategies to carefully control drying. By monitoring the product or the effluent, it is possible to determine the endpoint based either upon the rate of solvent removal or the amount of residual solvent in the product.

Crystallization

A recent review of the study of crystallization process using Process analytical technology method notes that the sensor of such process involves the molecule Spectroscopic method of Raman, NIR, ATR, FT-IR spectroscopy. The use of Raman spectroscopy in combination with chemo metric data analysis was used to identify & quantity the amount of several polymorphic forms present in Ranitidine HCL Tablet. Protein crystallization has also been of some interest for PAT applications, because of the increase in structure-based drug design fuelled by the recent developments in genomics and proteomics [16]

Pellet Manufacturing by Extrusion-Spheronization

An at-line process analytical technology (PAT) approach was used to increase the understanding of the solid-state behavior of the active pharmaceutical ingredients (APIs) during pelletization. Raman spectroscopy, near-infrared (NIR) spectroscopy, and X-ray powder diffraction (XRPD) were used in the characterization of polymorphic changes during the process. Samples were collected at the end of each processing stage (blending, granulation, extrusion, spheronization, and drying). Batches were dried at 3 temperature levels (60 0C, 100 0C, and 135 0C). Water induced a hydrate formation in both model formulations during processing. NIR spectroscopy gave valuable real-time data about the state of water in the system, but it was not able to detect the hydrate formation in the theophylline and nitrofurantoin formulations during the granulation, extrusion, and spheronization stages because of the saturation of the water signal. Raman and XRPD measurement results confirmed the expected pseudopolymorphic changes of the APIs in the wet process stages. The relatively low level of Raman signal with the theophylline formulation complicated the interpretation. The drying temperature had a significant effect on dehydration. For a channel hydrate (theophylline), dehydration occurred at lower drying temperatures. In the case of isolated site hydrate (nitrofurantoin), dehydration was observed at higher temperatures. To reach an understanding of the process and to find the critical process parameters, the use of complementary analytical techniques are absolutely necessary when signals from APIs and different excipients overlap each other.[17] NIR method was developed and validated for determination of active content ranging from 80-120% of the usual active content of the uncoated pharmaceutical pellets.[18]

CONCLUSION

PAT can be viewed as a constellation placing greater or less emphasis on a given activity depending on the current problem or situation

there is no written rule or straightforward path to progress through PAT. Experience and expertise are necessary, together with a good knowledge of the pharmaceutical environment. Once a pharmaceutical company has decided to implement PAT, continuous management support for the development and Maintenance of PAT - related activities is critical. It is a strategic and necessary step for the future success of PAT to encourage, stimulate, and initiate scientific collaboration and interaction as well as the relevant education and training.

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