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Implementation and Application of Process Analytical Technology in Pharmaceutical Industry

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ABSTRACT

In pharma industry quality is important.Drug quality depends more on production, best development, storage, and distribution strategies. PAT focuses on the principles of building quality into the product and process as well as continuous process improvement. PAT is based on belief that quality cannot be tested into the products it should be built in or should be by design. PAT promises to provide benefits to both consumers and manufactures of pharmaceutical products. Such technology will improve manufacturing efficiency while enhancing process understanding. PAT is the process of understanding and control it is not easy to implement. For successful implementation of PAT co-ordination, flexibility, communication between the staff is very important. PAT processes are deemed successful on the basis of significant process understanding. PAT is applied in every step of manufacturing of pharmaceutical product. PAT generally uses pioneering technologies like FTIR, NIR, ATIR, NMR.

Keywords: Process Analytical Technology, Tools of PAT, applications of PAT, quality in Pharma

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INTRODUCTION

In Pharmaceutical industries quality is very important. There has been a growing awareness for the significance of the quality of the pharmaceutical products. This awareness is represented through the appearance of various guidelines and definitions. For the management of manufacturing, quality testing of the products various new innovations such as TQM, QBD etc have helped pharmacists to manage their process more efficiently. In addition to all these there is a new technique which brings major change in manufacturing and quality testing of products called as Process Analytical Technology[1,2]. PAT is based on belief that quality cannot be tested into the products it should be built in or should be by design. Process Analytical Technologies (PAT) gives a system, which is 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. It focuses on building quality into the product through manufacturing process. PAT allows for and encourages continuous process manufacturing improvement. It includes physical, microbiological, chemical, and mathematical and risk analysis conducted in an integrated manner. 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. PAT provides a basis for identifying and understanding relationships among various critical Formulation and process factors and for developing effective risk mitigation strategies. PAT promises to provide benefits to both consumers and manufactures of pharmaceutical products. Such technology will improve manufacturing efficiency while enhancing process understanding.[1,2,4]A process is considered well acknowledged when All major sources of variability can be identified and explained; variability is managed by the process;[3] and product quality attributes can be accurately and reliably predicted over the design space established for materials used, process parameters, manufacturing, Successful implementation of PAT requires the appropriate selection of a process analyzer. One of the most significant challenges is the time it takes to analyze compared to the time that is available for making decisions for a step before proceeding to the next unit operation.[3]PAT is intended to support innovation and efficiency in pharmaceutical drug design, manufacturing and quality control and is being seen very imp tool for quality by design. Success of PAT depends to a large extent on efficient control of manufacturing processes to achieve predefined quality of the final product. This requires timely and accurate measurement of the critical attributes of the raw materials and process parameters

and implies that capability of the analytical methods and their selection are critical for successful implementation of PAT. In this article, we reviewed the various analytical methods that enable the use of PAT. 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 granules, blends, and other stages in the process. Through the use of probes in the manufacturing process, drying, uniformity and mixing endpoints, and other process can be checked with certainty. Sampling error would be minimized with in-line probes placed strategically throughout the production process. The PAT framework is founded on process understanding to facilitate innovation and risk-based regulatory decisions by industry and the agency.[3,4,2]

Implementation of PAT

PAT is the process of understanding and control it is not easy to implement. Process Analytical Technology (PAT) involves fundamental changes to working and manufacturing practices. It is based on the application of sophisticated and high technology process analyzers and the development of online Multi-Variate Analysis (MVA). Analysis of the process data is a key to understand the process and keep it under multivariate statistical control. there are some beneficial opportunities for the implementation of PAT tools processes that have long processing times, low efficiency, or generate high levels of waste new products, where PAT can provide more data for use in development and scale-up processes which have to be improved enough to compete with generic drug manufacturers once the time of market exclusivity ends. Installation of a real time instrument is not always the goal or outcome of the project most PAT processes are deemed successful on the basis of significant process understanding, which can be achieved during the development of project life cycle. A real time process instrument can either be implemented in routine production or be used as a reach back capability for diagnostic purposes during adverse production events. PAT projects fail or succeed based on degree of attention to detail and planning. PAT team should include experienced plant operators who are involved throughout the development of life cycle. To support PAT FDA created, a PAT committee composed of senior pharmaceutical and generic manufacturers; government officials; and private and academic consultants to the pharmaceutical industry. A PAT Research Team in the Office of Testing and Research, which conducts research to provide a scientifically based policy development process and support for the PAT Team. FDA has also published a PAT initiative. FDA has created a PAT Team to approach to CMC review and CGMP inspection.

For Successful Implementation of Pat

1) In order to design a process that provides a consistent product the Science based understanding of the chemical and physical properties of the proposed drug product and well through knowledge of process must be understood.

2) Science of analyzing drug product and other chemicals should be latest, it should not consume time, reduce paper work, and the instruments should be capable of elemental analysis. Such as FTIR, NMR.

3) Some smart experiments should be carried out, and high process knowledge is very important. Effective analysis, control and process understanding is important to realize financial rewards.

4) Smart and skilled staff, effective co-ordination and pit-stop working, meaningful and step by step process implementation is necessary.[6]

5) The validation plan for a PAT system is very important. It will typically include the validation of Process analyzer hardware and software, Software packages for data analysis, Process control software and IT systems for the management, storage and backup of results.

6) Increasing automation to improve operator safety and reduce human error. Facilitating continuous processing to improve efficiency and manage variability. Improving energy and material use and increasing capacity.

7) The implementation of PAT within the organizational structure requires accountability, roles and responsibilities to be specified (clearly defined process owners, project managers, subject matter experts, and process analysts).[7]

Strategy for Implementation of Pat

For successful implantation of PAT co-ordination, flexibility, communication is very important. While implementing PAT there should be a multidisciplinary approach. For implementing PAT there should be opportunity for live feedback and process control, cycle time reduction and laboratory test replacement as well as risk mitigation[8]. Strategies should accommodate the attributes of input materials, the ability and reliability of process analyzers to measure critical attributes, and the achievement of pre-established process endpoints to ensure consistent quality of the output materials and the final product[9]. In order to successfully implement PAT, a combination of sequential steps is essential.

Figure1- Steps of PAT

The organization should identify the whole procedure and understand it. Critical process Attributes should be understood. After identifying the critical attributes the organization should design and measure the attributes. Product quality and performance are ensured through the design of effective and efficient manufacturing processes. The organization should monitor steps and understand it thoroughly. Variability should be managed by the process. The analysis step ensures that once we have identified our critical quality points and monitored them, we can analyze it. This step includes the development, verification, and validation of any statistical models that could define the process. At-line, in-line, off-line testing is very imp in PAT. After analyzing overall process and developed any system foe analyzing it or developed any statistical tool. Continuous monitoring of critical attributes and performance record should be reported[9]. Differences in process analytical measurement and laboratory measurement.

Table 1: Process Analytical Technology Tools

Process analytical measurement	Laboratory Measurements
It is a automatic measurement	It is complicated to use and require trained analytical chemist for operations
Samples need not be pre-treated prior to Measurement	Samples may be pre-treated prior to measurement to improved selectivity or sensitivity
Rapid measurement	Slow measurement

There are many current and new tools available that gives scientific, risk-managed scale-up pharmaceutical development, quality controlled manufacturing, and quality assurance. when all these tools used within a system can provide effective and efficient means for acquiring information to facilitate process understanding, develop risk-mitigation strategies, achieve continuous improvement, and share information and knowledge. The key is to integrate PAT tools in the supply chain management from R&D to commercial manufacturing and use them to improve quality consistency, shorten cycle times, and minimize losses. Thereby, benefits can be

quantified in an appealing way[10,11]. There are three beneficial opportunities for the implementation of PAT tools:

1) Processes that have long processing times, low efficiency, or generate high levels of waste.

2) New products, where PAT can provide more data for use in development and scale-up.

3) Processes which have to be improved enough to compete with generic drug manufacturers once the time of market exclusivity end[12,13]

In the PAT framework, these tools can be categorized as:

1) Multivariate data acquisition and analysis tools

Pharmaceutical manufacturing process is too complex and it is a multifactorial system. There are many different development strategies and methods and instruments that can be used to identify optimal formulation and process conditions for these systems. By the use of this tool many methods and instruments are used for data acquisition. Experiments should be conducted to acquire knowledge and this knowledge should be used to understand product life cycle. It has been indicated that multivariate statistical process control can be a powerful tool for pharmaceutical applications and that real time and off-line measurements from analytical technology can be combined with process data to provide a robust tool for real time process monitoring.

2) Continuous improvement and knowledge management tools

Continuous learning is very important for any PAT projects throughout is life cycle. Data can contribute to justifying proposals for post-approval changes including introduction of new technologies.

3) Modern process analyzers or process analytical chemistry tools

In the modern pharmaceutical manufacturing chemical analysis of the product is very imp. In line and at line testing is very important. The physical and chemical properties of product should be tested such as temp, press. off-line in a laboratory at-line in the production area, during production close to the manufacturing process.

On-line where measurement system is connected to the process via a diverted sample stream; the sample may be returned to the process stream after measurement.

In-line where process stream may be disturbed (e.g., probe insertion), and measurement is done in real time.

4) Process and endpoint monitoring and control tools

In the formulation and optimization of drug products control is necessary. For the efficient manufacturing process should be modified and design process control that provide adjustments

to ensure control of all critical attributes. Proper strategies should be there for measuring quality of raw material. A good and reasonable combination of some, or all of these tools may be applicable to the single unit operation or to an entire manufacturing process and its quality assurance.[14, 15, 16,]

Pat Benefits

Handles complex unit operations with new techniques

Biotech industry have also realized the importance of PAT. Bio processing unit operations are too complex to control without management. Implementation of PAT techniques gives understanding of process and easy implementation of all process[17]. PAT involves replacing current laboratory-based systems with online sensors.[18] Such as it replaces the lab testing of drugs by IR, NMR Techniques which reduces time and saves money. This also reduces cost by eliminating old time consuming, high man- power requiring tests. For ex. Analysis of organic content of waste water is done in PAT by NMR and statistical tool is partial least squares calibration. It is the less time consuming and cost effective method. 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.[19]

Reduces time

Major application of PAT in the new product market is to reduce development time by reducing the gap between R & D and manufacturing. It provides enhanced product quality. However these applications are balanced by the requirement of a higher level of process understanding for designing steps in process and increased operational complexity for implementation.[20]

Industry Benefits

1) PAT reduces manufacturing costs of drug products by decreasing productivity and greater availability of production equipment.

2) PAT is the bridge for gap between R & D, Manufacturing, QA ,QC and IT departments. PAT gives smart experiments related to R&D and manufacturing. And provides an easy scale-up.[21]

3) PAT reduces paper work in industry and light submission.

4) It improves capacity of a process, if earlier capacity of a process was 30 it increases up to 70.

5) PAT reduces routine analysis, end product testing, stability testing and re-testing by testing the drug product while manufacturing and it also reduces regulatory involvement.

6) PAT gives real time data acquisition and integration.[22,23,24]

7) Increasing automation to improve operator safety and reduce human error.

8) Facilitating continuous processing to improve efficiency and manage operator variability.

Applications of Process Analytical Technology

Several types of PAT applications can accompany the life-span of a product or process. Major application 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[25,26]. PAT aims to ensure that all sources of variability affecting a process are identified, explained and managed. PAT provides improvement in quality also gives increased regulatory compliance and increase product uniformity which ultimately gives customer satisfaction. Use of proper techniques by PAT gives reduced waste, menace reduced environment impact.

Table 2: PAT Techniques used for Unit Operations

Unit Operation or Process Step	Technique
Raw Materials, Dispensing	NIR, Raman, Particle Size
Roller compaction process of dry granulation	Thermal effusively measurement during the effusively sensor
Crystallization	Mid-IR, Raman, NIR, FBRM, PVM
Simultaneous monitoring of solute concentration and Polymorphic state of crystal	Raman spectroscopy &Attenuated total reflectance(ATR) and FTIR
Analysis of organic content of waste water	NMR Spectroscopy
Wet Granulation	NIR, FBRM, PVM, Acoustics, Particle Imaging
Compression	NIR, NIR imaging, Raman, LIF, Raman, LIBS, Tetra hertz
Rapid and accurate tablet identification	Acoustic resonance spectroscopy
Analysis of liquid formulations containing sodium chloride	Laser induced breakdown spectroscopy

1) Raw material identification and quality control- In PAT Near Infrared Spectroscopy is used. This is very fast and effective method, for easy identification of raw material. Other lab methods consume time. And ultimately if time is saved money is saved in industry.

2) Simultaneous monitoring of solute concentration & polymorphic state of crystal- in PAT, Raman spectroscopy & Attenuated total reflectance (ATR) & FTIR used to know how the rate of addition of reactant affects the polymorphic state of crystal. And ATR & FTIR gives correct and accurate results.

3) Granulation- In PAT dry granulation end point is analyzed by temperature sensor. And wet granulation is determined by NIR-SR. In line testing is done for dry granulation and on- line testing is done for wet granulation.[27]

4) Compression-In PAT Analysis of API in tablet is done by NIR-SR, offline testing is done. Content uniformity is also tested by NIR-SR. This technique gives assurance that tablet is uniform.

5) Packing component identification- In PAT identification of blister PVC films is done by NIR-SR. it reduces many lab tests, which consume time. This testing is off-line.

6) Crystallisation– Crystallisation of pharmaceutical active ingredient is the most critical and least understood pharmaceutical manufacturing process. PAT involves scientifically based process design and optimization, statistical and information tools.[28,29]

7) Replaces old techniques to new techniques-PAT involves replacing current laboratory-based systems with online sensors. Such a it replaces the lab testing of drugs by IR, NMR Techniques which reduces time and saves money. This also reduces cost by eliminating old time consuming, high man- power requiring tests. For ex. Analysis of organic content of waste water is done in PAT by NMR and statistical tool is partial least squares calibration. It is the less time consuming and cost effective method.

8) Facilitating continuous processing to improve efficiency- PAT increases automation to improve operator safety and reduce human errors. It identifies and measure critical material and process attributes relating to product quality. It prevents scraps, rejects, re-processing by testing the product at various stages while preparing. It designs process control that provides adjustments to ensure control of all critical material and process attributes.

9) Moisture determination- In PAT various techniques are used for moisture determination. Radiofrequency, microwaves are used for moisture determination. NIR spectroscopy can also be used for moisture determination.[30]

10) API production by fermentation - In pharma generally antibiotics are produced by the use of fermentation. PAT helps in monitoring, control and significant enhancement of process understanding. Combining different types of multistage process information provides the possibility to predict the nominal titer of antibiotic fermentation.[31,32,33]

CONCLUSION

The main aim of the PAT is the quality cannot be tested into products it should be built in. The key components of this knowledge-based approach are better understanding of the product manufacturing process, analytical tests and data, process analytical tools, process monitoring, and continuous feedback during the manufacturing process. For successful implementation co-ordination between the staff, flexibility and communication is very important. The use of process

analytical technology can provide huge benefits to those who choose to use the technology. Such as the pharmaceutical industry and life science industry have widely accepted and applying it. And increasing product quality while delivering superior asset utilization and financial value. The goal of PAT is to encourage the industry to adopt innovative technologies to increase quality without raising concern that a new approach will lead to validation risks and production delays.

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