WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 5.990
Volume 4, Issue 12, 852-875. Research Article ISSN 2277– 7105

PROCESS ANALYTICAL TECHNIQUE

Kamble Santosh. M*, Gholve S.B, Sayyed Sarfaraz Ali, Ganesh Surkute, Tanaji Nirmal, Amol Duve

Department of Quality Assurance, Channabasweshwar Pharmacy College, Latur.

Article Received on
02 Oct 2015,

Revised on 25 Oct 2015,
Accepted on 17 Nov 2015

***Correspondence for Author**
Kamble Santosh. M
Department of Quality Assurance,
Channabasweshwar Pharmacy College, Latur.

ABSTRACT

Process Analytical Technology (PAT) is a system for designing, analyzing, and controlling manufacturing processes based on an understanding of the scientific and engineering principals involved, and identification of the variables which affect product quality. The PAT initiative is based on the FDA (The US Food and Drug Administration) belief that: "quality cannot be tested into products; it should be built-in or should be by design." Process Analytical Technologies (PAT) are used to provide and inform timely analysis of critical quality parameters with the end goal of improving final product quality as well as reducing manufacturing costs, thereby significantly benefiting the Pharmaceutical Industry in manufacturing area. 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, Historical view, Regulatory view, PAT tools, Pat implementation and a review of their application in the wider pharmaceutical industry. The first steps in an Analytical Quality-by-Design (AQbD) method development include understanding the analysis needs (e.g., purpose, specificity, sensitivity, cycle time, on-line/off-line, qualitative/quantitative, accuracy, precision) and selection of the technique that will meet these criteria. One set of analytical tools applied during the development and scale-up of drug substances and dosage forms include in-situ analytics, chemometrics and modelling i.e., Process Analytical Technology (PAT) tools. Pharmaceutical companies face many challenges and problems while implementing PAT into their new and pre- existing manufacturing processes. This article discusses the challenges and problem encountered. The scope of this article is to introduce the reader to PAT. It, however, is a wide – ranging subject, which is expanding rapidly

KEYWORDS Process analytical technology, Quality by design, critical quality attribute.

INTRODUCTION

The current process analytical technology (PAT) initiative underway within FDA exemplifies the latest consortium between FDA and the industry that aims to encourage the concepts of quality by design, use of computerized data gathering and evaluation techniques, and process- and product-monitoring methods through advanced instrumentation and data evaluation. Although this partnership between FDA and the industry is relatively new (2001), methods related to PAT such as chemometrics have been studied and have been in use for quite some time.Yet, the PAT initiative has raised several questions:What does PAT really encompass? Is it a new technology or is it a series of proven scientific principles? How can PAT be used in a pharmaceutical operation to gain better process understanding and possibly reduce cycle times and associated costs? This article discusses the concepts that embody PAT. Emphasis is placed on chemometrics, which is the use of mathematical and statistical models to extract and interpret chemical data.

Historogical, pharmaceutical production involves the manufacture of the finished product, followed by laboratory analysis to verify quality of the product. The disadvantages associated with this approach are continual process optimization, recurring manufacturing difficulties, and the possibility of failed batches.

The Food and Drug Administration (FDA) is inviting discussions throughout the pharmaceutical industry concerning a new mode of operation, which will address these concerns. This mode of operation is known as Process Analytical Technology (PAT). 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.

The PAT initiative was first proposed by the United States Food and Drug Administration’s (FDA), Centre for Drug Evaluation and Research (CDER) with the objective of achieving good health and cost benefits by application of modern process control and tests in pharmaceutical manufacturing industries.

Quality-by-Design (QbD) is well-established in development and manufacture of pharmaceutical drug substance and drug product and is discussed in ICH Q8, Q9 and Q11.

The outcome of QbD is a well-designed and understood quality product that consistently delivers the continuous performance. The knowledge obtained during development helps in justify the establishment of a design space, (process) control strategy and set point within the (regulatory approved) design space. Materials made within the design space will produce an acceptable product, and the changes within the design space are (regulatory) acceptable. These same principles and concepts have been applied to the development of analytical methods, and termed Analytical QbD (AQbD). Analogous to process QbD, the aim of AQbD is to design a well-understood, robust method that consistently delivers the necessary performance as described in the analytical target profile (ATP). One set of analytical tools used in support of pharmaceutical development and control include insitu analytics, chemometrics and modelling i.e., Process Analytical Technology (PAT) tools. Process analytical technology (PAT) can be defined as "a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring final product quality".

This definition (and relation with QbD) has been debated and described in many venues (e.g., conferences, social media, article etc.). In these enthusiastic discussions, one point that is frequently overlooked is that PAT tools are firmly attached in the pharmaceutical workflows that underpin development and scale-up, for both drug substance and dosage forms. The term Process Analytical Technology (PAT) was introduced by the US FDA as an initiative to bring an improved understanding of pharmaceutical manufacturing processes to increase the quality of their products.

Process Analytical Technologies involve the use of raw material properties, process monitoring, manufacturing parameters and chemometric techniques to produce finished products of acceptable quality and purity. The central point of PAT is to generate product quality information in real-time. Process monitoring traditionally involved temperature, pressure, flows, pH and other physical parameters, PAT focuses on the use of in-line testing using near infrared, Raman, or other physiochemical techniques as a primary means of process monitoring. The advantages of PAT are many and varied. 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.

The first step away from off-line testing (laboratory separated from the production plant), would be at-line testing. This is the movement of process testing instrument to the production line to provide fast and quality results. One advantage is elimination of the transfer of samples which involving time delays. Along with traditional tests such as Dissolution, Assay, Friability, Hardness, and Thickness, this could also include accelerated dissolution rate analysis, and NIR tablet analyzers.

One approach of process analytical chemistry is on-line testing, which either draws samples or monitors periodically. Another mode is known as in-line testing, which places probes in constant contact with drug product and formulation. The advantage of on/in line testing is better controller of the process. Beyond data such as blending, or drying, the FDA has proposed creating on/at-line assurance of dissolution rates using analytical data correlations. Near infrared (NIR) is one of the techniques that has gained recent recognition as ameans to add on or in-line analysis at the production level.

The near-infrared light does not destroy or react with samples and is able to penetrate into and throughsolid samples. While NIR has gotten most of the attention, PAT is not limited to NIR but can include many other monitoring instruments, such as Raman, Mid-IR, acoustic emission signals, and other imaging techniques Dissolution is the first most important method for evaluating solid oral dosage form consistency, and uniformity. Using PAT, processes would be under such high control that the dissolution results could be accurately predicted well before the drug product and formulation are analyzed.

Research on the correlation between dissolution results and measured process parameters would be performed so that the impact of process, raw materials, and finished product variables can be understood. The manufacturing process could be continuously monitored and adjustments made to ensure that the finished product would meet the desired specific quality and criteria.

A process is generally considered well understood when

1. All critical sources of variability are identified and can be explained

2. Product-quality attributes can be accurately and reliably predicted over the design space established for materials used process conditions, manufacturing, environmental etc
3. Variability is managed by the process.

The objective for PAT implementation of the following.

-Better process understanding & Improved yield because of prevention of the scrap, rejects, and reprocessing etc.

- Reduction in the production cycle time by using online/ at-line or in-line measurements and control.

- Decrease in the energy consumption and improved efficiency from conversion of the batch process into a continuous process in the manufacturing process Cost reduction because of reduced waste and reduced energy and electric consumption in the manufacturing area

MATERIAL AND METHODE.

PROCESS ANALYTICAL TECHNOLOGY HISTORICAL,BUSINESS AND REGULATORY PERSPECTIVE

Pharma industry goal is to improve formulations so as to provide patients innovative and more efficient solutions, and thus achieve commercial break through. For this, improvements in existing technologies are required. The emerging PAT strategy is to guide the drug industry in achieving various goals. Process Analytical Technologies involve the use of raw material properties, manufacturing parameters, process monitoring, and chemometric techniques to produce finished products of acceptable quality. It facilitates and encourages the Introduction of innovative approaches. However, it is difficult to consider potential technological alternatives without critical review to replace well established techniques. 16

HISTORICAL VIEW OF PROCESS ANALYTICAL TECHNOLOGY (PAT)

Because they have been used for many years, existingexperimental methods and manufacturing processes and quality control parameters are considered well established and trusted to generate few difficulty and errors and make only simple contributions to process variation and different process parameters.

Historically, pharma lab develops a product, describe the product, improve the quality of product, maintain the quality of product for a sufficient time, describe the process materials and methods in great detail in the regulatory filing, and validate the process through various batches. The quality of the product would remain consistent as long as nothing was changed.

With this data industries are having little pressure to improve manufacturing efficiency and rate.

BUSINESS VIEW OF PROCESS ANALYTICAL TECHNOLOGY (PAT)

To pharma with its paper-based control systems PAT is different technology, but it is old that to industries such as food and beverage, petrochemicals and semiconductors etc. US drug companies have had the ability to use process control for 20 years, but they have not used it because it is more expensive in term of the cost of the equipment, the cost to develop qualification, validation and quality systems. There are no industry leaders yet demonstrating the value of PAT, so Pharma companies are approaching PAT with uncertainty. Although PAT increase production efficiency and rate, this may not be viewed from a business standpoint as a strong impetus for change due to the perception that the implementation costs may outweigh the return on the investment in various cases, especially for small pharmaceutical companies which manufacturing drug product and dosage forms that are already struggling with tight or nonexistent margins. With limited available capital, equipment, and talented human assets, maximizing asset utilization and return on assets is becoming vital to future success and survival.

Although benefits of PAT in the long-term are generally recognized, the short-term uncertainty and risk, at least in these early days of the FDA guidance, boil down to how much time and resources a company should invest in a pharmaceutical product that faces an uncertain future in terms of clinical efficacy, regulatory approval, and commercial success. Accounting pros and cons of technology companies should determine when the investment in process development does benefits the company and when it does not make any business sense. For example, a process step is not under any time constraints, does not represent a potential bottleneck, does not consume costly reagents and resources, and does not pose a risk of contamination or introduction ofimpurities, and then there may be little justification for investing in the monitoring, control, and optimization of that particular process step.

Further available analyzers are not suitable for Pharma industry which requires instrument development. The sensors available as analysis tools are not compatible with the process. Analyzer dependability, having small expertise in high specialized technology, inadequate validation of analyzer/software add with all these makes. PAT associated risks too high and creates hesitance over change and remains as big hurdles for PAT implementation. But business models are changing and the importance of manufacturing's role in the financial

performance of pharmaceutical companies are important. While the cost of restructuring production lines may be daunting to smaller companies, the savings gained from more efficient use of resources, reduced waste, faster product approvals and a lower risk of product recalls would outweigh the cost to implement PAT.

REGULATORY VIEW OF PROCESS ANALYTICAL TECHNOLOGY (PAT)

A major contributor to inhibition of PAT adoption is concern over how regulatory agencies will react to the technology during a facility review. If the technology requires the agency to develop an understanding of the potential impact on the product, this could result in a protracted approval of the facility and thus delay the introduction of a new product to the market.

Pharma industries are accepting new technology on the R&D side, "it lags behind on the manufacturing side for fear of delaying approval," There is concern within the industry that there is lack of worldwide harmonization of regulatory expectations relative to PAT that could lead to PAT being accepted by one regulatory agency while another might not share the same level of acceptance, resulting in quality control strategies that are specific to a given market. However FDA has participated in international conferences as a means of creating harmonization on the PAT approach. These types of activities should also be conducive to harmonization on the PAT approach. The agency's intention was not to dictate how companies should implement PAT, but rather to create a flexible regulatory process that would involve regular meetings with regulators, at which time companies could present and discuss individual strategies and innovative approaches. FDA does not intend to inspect research data collected on an existing product for the purpose of evaluating the suitability of an experimental process analyzer or other PAT tool. FDA's routine inspection of a firm's manufacturing process that incorporates a PAT tool for research purposes will be based on current regulatory standards (e.g., test results from currently approved or acceptable regulatory methods).Also companies are mostly considering utilizing PAT to show that their products are okay using existing processes, rather than redesigning and optimizing their processes, contends.

The pharmaceutical industry has been hesitant to introduce new technologies and innovative systems for a number of reasons one of which often cited is that— in the FDA's own words—"The existing regulatory system is rigid and unfavorable to the introduction of new technology." Industry's concern is that an increased amount of process data and cost may

highlight problem in a product. The more in depth process assessment by on-line analytical measurements may lead to an increased number of products failing to meet their release criteria. These same products might not have failed utilizing the current off-line methods of analysis. Another concern is redefining the product specifications considering the more accurate statistical data provided by on-line measurement techniques. Though PAT is not regulatory law, the FDA pretty much insists that it be adopted. FDA introduces guidelines, which are not legal documents, but they want you to follow the guidelines in manufacturing industries. Numerous analysts have commented that regulatory guidelines have a tendency to become laws, and it is probably better for companies to try to stay ahead of the curve by taking a proactive stance. 2

BASIS FOR PROCESS ANALYTICAL TECHNOLOGY

Despite the fact that the FDA's PAT framework (and guidance) 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 etc. 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 and novel manufacturing science.

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 in to the production area. Although industrial process analyzers have been in use for more than 60 years, the modern period of PAC essentially began with the formation of the Centre for Process Analytical Chemistry (CPAC) in 1984 , the goal of PAC is to " supply quantitative and qualitative information about a chemical process "for monitoring, control, and optimization: they went on to define five " eras " of PAC:1) off line, (2) at line, (3) online (4) inline, and (5) non-invasive, which describe the evolution of sensor technologies in industries. The industrial PAC movement has been bolstered by two decades of advances in materials science, electronics, and chemo metrics etc. Since the inception of CPAC the pace of innovation in sensors, instrumentation, and analytics has quickened dramatically. The development of more robust, sensitive photo detector materials, micro electro mechanical systems (MEMSs), and fiber optics and the perpetual advancement of computing power (as predicted by Moore's law) have both increased the performance and

reduced the cost of PAC. As a result, PAC is now a critical part of routine operations within the industrial chemistry.

PAT TOOL BOXES

PAT tools are routinely applied to develop a greater understanding of the process design space under a Quality-by-Design (QbD) framework. The use of PAT tools helps enable the development of robust processes, processes that are well-understood, with process set points that are controlled within design regions that are well-away from the edges of failure. As "quality cannot be tested into a product; it should be built-in or should be by design" well-designed and controlled processes may not require routine analytical measurements and feedback control during the manufacture.

A PAT tool that measures a critical quality attribute (CQA) may be implemented commercially for process control, however there are business drivers and regulatory aspects that will contribute and help to a final control strategy. Many on-line tools are routinely applied to monitor measure or control processes. Commonly used PAT tools that are well-integrated and routinely used in manufacturing include thermocouples and pressure sensors. Spectroscopic tools near infrared, mid infrared, Raman are utilized due to the specificity gained by the presence of functional groups routinely found in raw materials, intermediates and drug substances that are often not part of the matrix.

This specificity can allow for qualitative trending or the quantitative determination of the component of interest. Many tools are routinely applied to develop and understand the synthetic route. The choice of tool will be dependent upon the type of information required, timeframe of analysis, reaction matrix and chemical reactivity of the analytes of interest. Typical information desired will include rate of product formation (or reactant loss) and formation of impurities (from side reactions or chemical degradation). Measurements performed during isolation will include solvent levels, particle size/shape and polymorphic form. The resultant material may be milled if the particle characteristics are not appropriate for downstream processing. The finished API is subsequently put into a dosage form manufacturing process. Analogous to the first step of the API process, the first step is to confirm the identity of the ingoing dosage form materials (excipients and API). An added aspect of the dosage form identity test is an assessment of physical properties (e.g., particle size). NIR is often used to confirm chemical identity and physical properties. The tableting process is made up of a series of blending/ mixing/lubrication steps followed by compression

and film coating. In the early process steps, the homogeneity of the mixture is most important, and NIR is often used to determine homogeneity. During granulation steps, evaluation of polymorphic form change and wet granulation end point are commonly tested. Once the tablets are compacted, potency assessments are made of the finished product, and NIR and Raman are the most often employed spectroscopic tools. The types of coating measurements are dependent upon the film coat type, functional or elegance. Film coatings can be assessed for weight gain, or spectroscopic tools (e.g., terahertz, chemical imaging etc.) can be used to determine thickness.

API PAT EXAMPLES

Raman and mid infrared (MIR) spectroscopy are complementary techniques. Both have found widespread use in the development and scale-up of API. For example the reaction of a thiol dosed into a bromobenzene compound. Raman was chosen for this reaction, as there is a strong band at 292cm-1 (CBr vibration). Monitoring at 292cm-1 will show the debromination of reactant as it is consumed (either degraded or reacted) to form product38. The S-H band can also be monitored by Raman during this reaction. By monitoring at 2582cm-1, the addition of reactant can be monitored followed by its consumption.40 In this case, following the consumption of both raw materials, the endpoint can be determined and adjusted during process refinement. The Raman trend tells the chemist the reaction is dose controlled, and rapid. The entire reaction takes approximately 5 minutes from reactant addition to reaction completion.

DRUG PRODUCT CONTENT UNIFORMITY (CU)

NIR is used for dosage form potency assessments (content uniformity testing) and Raman is also finding use. 41 The samples can be evaluated by qualitative trending, or a quantitative determination can be made. 42 As NIR is sensitive to both chemical and physical properties of the material, appropriate variance must be built into the model prior to use, and diagnostics used to ensure the test material falls within the model. 43 Calibrator tablets are generated for the purpose of systematically adding the variance to the model. 46 Typical sources of v Drug gariance will include API percentage, hardness, weight, water content, and excipient source.

DRUG PRODUCT BLEND MONITORING

The spectral homogeneity of blends can be easily monitored using near infrared (NIR) spectroscopy. 47 Note that the level of the API rapidly comes to steady state (spectral homogeneity) for all blends within approximately 75 blender rotations. With the NIR spectrometer, other components can generally be monitored as well. Although the uniformity of the blend is critical for a quality dosage form, blending is seldom a quality concern requiring the routine use of an on-line tool. The use of PAT is useful for fault detection and identification of root causes if manufacturing issues occur. 46

WATER CONTENT

NIR has very good specificity for water, and has found widespread use for this analysis. 49 If technically feasible, the same spectra used to confirm tablet identify can be re-purposed for the determination of water content and also tablet potency. The ability to rapidly test for tablet identity, potency and water content has contributed to real time release testing (RTRt). The data can be used for trending the water content in each vial, or with the creation of a calibration curve developed using a reference method (e.g., Karl Fischer), quantitative data for each vial. This type of non-destructive testing has significant advantages over destructive methods as the materials can subsequently be evaluated by other analytical methods. Consequently, this allows a 1:1 correlation of water data with another attribute (for instance purity).

FEED FORWARD CONTROLLERS

Raw material variability can be a significant factor to product variability in the absence process adjustments to account for this variable input.

The use of feed forward controllers can allow for the adjustment of the process within the design space to compensate for (or reduce the impact of) the raw material variability on the final quality attributes of the product.

This can be done prior to the initiation of the process (which differs from feedback controllers which modify process conditions based upon observations (measurements) during the process.

In the course of the development of the process, the impact of the raw materials can be assessed along with the process understanding DoE studies to achieve a correlation between the raw material attributes, process parameters and product quality attributes. 54

This PCA can be used to select material lots with differing properties for inclusion into DoE studies. Via development of simulators, process parameters can subsequently be simulated to minimize the resultant product variability prior to initiating the manufacture.
This approach can be utilized to reduce lot to lot product variability without the incorporation of in-situ analytics during the manufacture.

IMPORATANCE OF PAT

Cost control, resulting partly through more efficient production processes, and partly through the minimisation 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 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 preparation.

As a direct consequence of the "cGMPs for the 21st Century" initiative, the pharmaceutical industry is experiencing pressure from the regulator to address concerns around limited process understanding, process inefficiencies and continuous process improvement through the adoption of PAT. Since FDA released its PAT initiative, few pharmaceutical companies are willing to talk about their efforts to implement PAT.

To encourage industry for PAT implementation FDA introduced the "safe harbor" or "research exemption" concept which is designed to encourage the industry to investigate tools that will provide increased process information without the fear of having a negative impact on the ability to release products that meet all aspects of the company's current quality control strategy.

Scientists at Sigma-Aldrich Biotechnology used a DOE approach to develop a cell culture medium optimized for a variety of Chinese hamster ovary (CHO) cell lines, which biopharmaceutical firms use to produce protein-based biologics. The researchers used statistical software to identify the best-performing culture media in their arsenal and develop methods to further increase cell growth and productivity It is a highly selective method

that allows researchers to easily and accurately determine the active pharmaceutical ingredient (API) content of a formulation while largely ignoring the physical parameters of the samples or sampling conditions.

PAT IMPLEMENTATION

Key difference between current practices in pharmaceutical manufacturing and a PAT approach.

-The use of novel analytical technologies and process.

-The establishment of multifactorial relationships between materials, process and environmental conditions, and an understanding of the consequences of these relationships for product quality and process robustness in manufacturing areas.

-The use of knowledge management tools.

Four key elements in PAT implementation

1. Building a science – based knowledge base complete process understanding at the mechanistic and firstprinciple level

2. Process monitoring and control determination of critical process parameters and critical quality attributes and selection of measurement, analysis and control mechanisms to adjust the process to provide the predicted quality of the product.

3. Validation of PAT system.

4. Regulatory strategies.

1.BUILDING A SCIENCE – BASED KNOWLEDGE BASE

The PAT guidance emphasizes the need to develop a deep understanding of the underlying scientific principles behind pharmaceuticals manufacturing processes to determine the parameters critical to process and product quality. The knowledge base provided by the PAT approach is valuable in three main ways.

-It is a foundation for robust process and product Design

-It facilitates continuous learning throughout the product

-It is supports and justifies flexible regulatory paths

for innovative new approaches.life cycle

Examples of sources of variation

-Variation in the raw material supplier manufacturing processes that impact the chemical and physical attributes of the supplied materials

-Time based variation in manufacturing performance (e.g., between equipment maintenance events).

2. PROCESS MONITORING AND CONTROL

The understanding of the interaction between process and product is the basis for the design of the process monitoring, process control and QA strategies used in manufacturing PAT is an integrated approach in which the results obtained from the real time analysis of critical process control points are used to control the process in some way. During manufacturing, process parameters are adjusted (within clearly defined limits) to produce the desired product quality attributes at the process end point.

3. VALIDATION OF PAT SYSTEM

The validation plan for a PAT system will typically include the validation of

-Software packages for data analysis

-Process analyser hardware and software

-Process control software

-IT systems for the management, storage and backup of results

4. REGULATORY STRATEGIES

A PAT policy development team of four subject matter experts has been established to work with industry to facilitate discussion on proposed pat approaches at an early stage and support FDA's sciences and risk based approaches to PAT. PAT is a joint initiative of the centre for Drug Evaluation and Research (CDER), Office of Regulatory Affairs (ORA) and the Centre for Veterinary Medicine (CVM) within the "cGMPs for the 21st Century" framework.

PAT APPLICATION IN THE PHARMACEUTICAL INDUSTRY

Innovations in the process analytical chemistry (process analyzers) 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.68 A variety of analytical techniques have been used in the pharmaceutical industry, including Fourier

transform infra-red spectroscopy (FTIR), UVspectroscopy, gas chromatography, high performance liquid chromatography (HPLC), X-ray diffraction spectroscopy, and NIR spectroscopy.

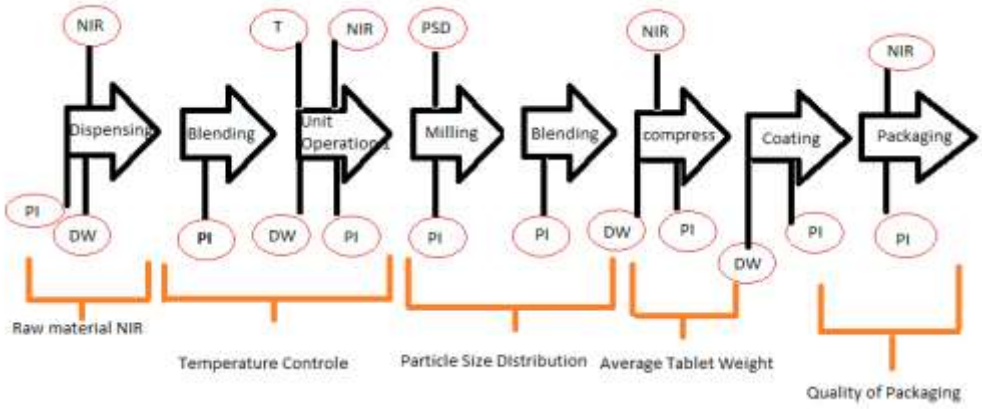

Figure 1 illustrates a typical tablet manufacturing process in a pharmaceutical process.

PSD: Particle size distribution; T: Temperature; DW: Dry weight; PI: Product impurity. Figure 1: The different unit operations that comprise a typical pharmaceutical process. Each step can potentially benefit from implementation of one or more PAT applications.

Table 1: Examples of PAT applications in the pharmaceutical industry.

Application	Process analyzer	Statistiacl tool	Observation
Rapid, accurate and continuous tablet identification	Acoustic resonance spectroscopy	Principlecomponents Analysis (PCA)	A fast and non-destructive method for on-line analysis and label comparison before shipping, to avoid mislabelling ofdrug.
Evaluation of content uniformity for low-dose tablets	NIR	PCA	NIR/PCA was used to predict content uniformity of low-dose tablets manufactured by a direct compression process. 58
Determination of content of uncoated pharmaceutical Pellets	Near infrared	Partial leastsquares (PLS) analysis	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
Roller compaction process of dry Granulation	Thermal effusivity measurement using the effusivity sensor	-	Effusivity measurements were used to monitor the roller compaction process.
Mechanical property	Air-coupled	Iterative	Examination of the vibrational

determination of the tablet containing drug	excitation and laser interferometric detection	computational technique	resonance frequencies can be directly correlated with the mechanical properties of the tablet providing a non- destructive technique for physical characterization of the tablet.
Powder flow characterization	NIR	PLS	Real time information on the flowing cohesive powder Mixture was used to avoid powder segregation or agglomeration and thus to maintain product quality. 62
Analysis of sustained-release tablet film coatings using terahertz pulsed imaging (TPI	Terahertz pulsed spectroscopy (TPS)	-	Tablet coating thickness, coating reproducibility, distribution, and uniformity can be easily determined. The method was validated against optical microscopy imaging
NIR measurement of the potency of an API	NIR	PLS	Potency of heparin active pharmaceutical ingredient was determined by this non-destructive method.
Active drug identification and content determination	NIR	PLS	NIR method was used for qualitative and quantitative determination of ranitidine in granules for compression, cores, and final tablet. 65
Monitoring capsule manufacturing at small-scale level	NIR	PLS	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. 66
Analysis of liquid formulations containing sodium chloride	Laser-induced breakdown spectroscopy (LIBS)	PLS	Method does not need any sample preparation and it is less time-consuming.
Quantification of the active ingredient in pharmaceutical injectable formulations	NIR and UV–visible spectroscopy	PLS	More economical and less time-consuming and more beneficial method for quantification of the lysine clonixinate
Prediction of dissolution for a sustained-release dosage form	NIR	PLS	This method was used to identify differences in the composition of the coating polymers used for a tablet and thus assist with prediction of dissolution behaviour and process. 69

It is seen that PAT approaches could be applied to the various unit operations in the process: dispensing, blending, milling, compression, and tablet coating and packaging. NIR provides a means of quick and reliable testing of raw material quality such that only those raw material lots that meet the required specifications would be used during processing. In-line temperature monitoring of the performance of the extrusion step could be used to control the step via a feedback loop to the heating/cooling system that controls the temperature. Further, particle-size distribution will be continuously monitored during milling for process consistency and controlled via feedback or feed forward control. The weight, thickness, potency, and hardness will be tested at line at the tablet press for continuous quality verification and feedback control of compression. This approach will enable both increased process understanding and process control in manufacturing. Table reviews some recent PAT applications in the pharmaceutical industry. Include process analyzers, NIR is the most popular and is used in a diverse set of applications including estimation of active content powder-flow characterization, raw material analysis, and dissolution rate. Some other analyzers that have been reportedly used include acoustic resonance spectroscopy, air coupled excitation and laser interferometric detection, terahertz pulsed spectroscopy, effusivity sensor, and laser-induced breakdown spectroscopy. It is evident from the diversity of the analytical tools that are available and their capabilities that a part of the vision outlined in Fig. can be realized, i.e. the process can be designed such that at the end of each step, assurance can be provided that the step performed its function in a satisfactory manner. However, examples of using the information from the analyzers to change the operating conditions and bring the process back in control are not too common and creation of such control schemes is likely to be the focus of the pharmaceutical industry in the future.

PAT APPLICATION AT FOLLOWING SITES

-RM Testing (warehouse based)

-Packaging Components

-Blending (at- line or on- line)

-Drying

-Tableting (potency and CU)

-Encapsulation (Coating thickness)

-Packaged product

-Equipment cleaning

-Equipment cleaning (surface monitoring).

CONCLUSION

The aim of a PAT approach should be to implement robust processes that are flexible enough to accommodate a defined level of variability in process materials (physical and chemical attributes) through adjustment of the process conditions. A knowledge base created through the collection, analysis and evaluation of research, development and manufacturing data facilities the justification for a science and risk based approach to analytical method validation and process monitoring and control. As can be seen in the above discussion, the use of PAT techniques can be a huge benefit to those who choose to use the technology. Process Analytical Technology provides better knowledge of raw materials, manufacturing parameters and their impact on finished product quality. This will result in a more robust process, better products, more uniform dissolution results, and a huge cost savings for the manufacturer. The challenge that dissolution scientists face is to become familiar with this next generation of pharmaceutical testing and its potential applications in pharmaceutical testing. that dissolution scientists face is to become familiar with this next generation of pharmaceutical testing and its potential applications in pharmaceutical testing.

REFERENCES

1. U.S. Department of Health and Human Services, Food and Drug Administration, www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/QuestionsandAnswers onCurrentGoodManufacturingPracticescGMPforDrugs/UCM071836 Accessed 13 may 2013.
2. U.S. Department of Health and Human Services, Food and Drug Administration A presentation at the Advisory Committee for Pharmaceutical Science by Dr. AjazS. Hussain. http://www.fda.gov/ohrms/dockets/ac/cder01.htm#Pharmaceutic al%20Science Accessed 13 may 2013.
3. U.S. Department of Health and Human Services, Food and Drug Administration Guidance for industry: PAT- a framework for innovative pharmaceutical development, manufacturing and quality assurance http://www.fda.gov/downloads/Drugs/Guidance ComplianceRegulatoryInformation/Guidances/ucm070305.pdf Accessed 25 may 2013
4. U.S. Department of Health and Human Services, Food and Drug Administration: Guidance for industry: PAT – a framework for innovative pharmaceutical development, manufacturing and quality assurance

www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070305.pdf, Accessed 25 may 2013.

5. Rathore, AS, Bhambure R, Ghare V, Process analytical technology (PAT) for biopharmaceutical products, Anal Bioana Chem, 2010; 398: 137–154.
6. Jarka G, Process analytical technology (PAT) for biopharmaceuticals, Biotechnol. J, 2011; 6: 369–377.
7. Winskill N, Hammond S, An Industry Perspective on the Potential for Emerging Process Analytical Technologies, FDA Science Board, Rockviile, MD, Nov. 2001; 16: 169-180.
8. Rathore AS, Process analytical technology (PAT), Trends Biotechnol, 2009; 27(12): 698-705.
9. Scott B, Wilcock A, Process analytical technology (PAT) J Pharm Sci Technol, 2006; 60(1): 17–53.
10. Rathore AS, Gerhardt AS, Montgomery SH, Tyler SM, Process analytical technology Biopharm Int, 2009; 22(1): 36–44.
11. Read EK, Park JT, Shah RB, Riley BS, Brorson 12. Park JT, Shah R, Brorson KA, Rathore AS, Process Analytical Technology scope, Biotechnol Bioeng, 2099; 105(2): 285–295.
12. Van Hoek P, Hamrs J, Wang X, Rathore AS, Quality by design for biopharmaceuticals, Wiley Interscience, Perspectives and case studies, 2009; 199.
13. Seely J, Rathore AS, Sofer G, Process validation in Manufacturing of Biopharmaceuticals, Taylor and Francis, 2012.
14. Rajabahadur VA, Dewangan P, Process Analytical Technology Helps Pharmaceutical Companies Capture Process Knowledge and Achieve Operational Excellence.
15. Banerjee S, Bhatwadekar N, Mahajan P, Karode P, Mishra A, Process Analytical Technology (PAT): Boon to Pharmaceutical Industry,available at http://www.pharmainfo.net/reviews/processanalytical- technology-pat-boon-pharmaceutical-industry Accessed on 25 may 2013.
16. Spiegel R, Pharma Industry Sees Process Innovation at Last, February, 2006; 38.
17. Rick EC and Egan JC, the Impact of Process Analytical Technology, (PAT) On Pharmaceutical Manufacturing, 2009.
18. PAT Initiative Expected to Invigorate Pharmaceutical industry with Improved Quality, Better Efficiency and Improved Profits, White paper, 1-8.

19. PAT-Ready production scale for the pharmaceutical industry from processing solution for the process industries, available at http://www.pharmainfo.net/reviews/process-analyticaltechnology- pat-impact Accessed on 25 may 2013.
20. Benson RS, McCabe JD A practical approach to PAT implementation-Pharmaceutical Technology, Pharm. Eng, July/Aug 2004.
21. A practical approach to PAT implementation Highlights of Advances in the Pharmaceutical Sciences: An American Association of Pharmaceutical Scientists (AAPS) Perspective2007.www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsa ndTobacco/CDER/ucm128080.htm Accessed on 25 may 2013.
22. Slow Adoption of PAT for Bio processing- Challenges Emanate for Technology Development and Design of Processes, genetic engineering and biotechnology news, (Vol. 26, No. 16), 2006, available at www.genengnews.com/gen-articles/slow-adoption-ofpat-for-bioprocessing/1891/ Accessed on 25 may 2013.
23. Scott P, Process Analytical Technology: Applications to the Pharmaceutical Industry, Quality Assurance Analytical Services, AstraZeneca, Westborough, MA available at www.dissolutiontech.com/DTresour/0802art/Article_1.htm Accessed on 25 may 2013.
24. Plant Automation in Pharma An Asian perspective, Process Analytical Technology Application in precipitation processes available at http://www.pharmafocusasia.com/manufacturing/pharma_pat_precipitation_process.htm Accessed on 25 may 2013.
25. Gifford J, Albee A, Deeds ZW, Delong B, Kao K, Ross JS, Caple MV,An Efficient Approach to Cell Culture Medium Optimization—A Statistical Method to Medium Mixing, Sigma-Aldrich Biotechnology, Available at www.statease.com/pubs/culture.pdf. Accessed on 25 may 2013.
26. Randall CW, PAT PendingTechnology Tools for Developing Improved Pharmaceutical Manufacturing Processes. Presented at the Advancing Manufacturing Summit, West Lafayette, volume 7, Issue 12, Dec 2004.
27. Bradley D, Bronwyn G, NIR Spectroscopy - Just One of Many Analytical Tools for PAT, Amer. Pharm. Rev, 2011; 3: 70-74.
28. Howard W, Sonja S, Michael J, Geraldine T, Frank J, Frank E, Timothy N, Paul K, On-Line Determination of Reaction Completion in a Closed-Loop Hydrogenator Using NIR Spectroscopy, Appl. Spec. 1998; 52(1): 17-21.

29. Santangelo M, Maranzano B, Norris K, McDermott T, Near Infrared (NIR) Determination of Uniformity for a Drug Product Powder for Oral Suspension (POS) in Amber Glass Bottles, Amer. Pharm. Rev, 2010; 68-72.
30. Mark Bell, NIR as an In-Process Tool, Amer. Pharm. Rev, 2008; 11(3): 75-79.
31. Frederick TM, Dolman S, Nyrop J, Peter J. Skrdla, On-line FTIR Monitoring and Simultaneous Optimization of a Strecker Reaction Performed in a Laboratory Scale Flow-Through Reactor, Amer. Pharm. Rev, 2011; 14(7).
32. Shelly L, Application of Online Reaction Monitoring by Raman and Infrared Spectroscopy in Early Development, Amer. Pharm. Rev, 2010; 62-67.
33. Sparen A, Johansson J, Svensson O, Folestad S, Claybourn M, Transmission Raman Spectroscopy for Quantitative Analysis of Pharmaceutical Solids, Amer. Pharm. Rev, 2009, 62-73.
34. Zhou Y, Crane N, Chunsheng C, Yanxi TC, Model for Raman Spectroscopic Monitoring of Process-Induced Pseudomorph Interconversion, Amer. Pharm. Rev, 2009; 56-64.
35. Salvas J, Simard JS, Abatzoglou N, Raman Spectroscopy to Analyze Intact Pharmaceutical Tablets: Factors Influencing MVPM based PAT Methods, Amer. Pharm. Rev, 2010; 46-53.
36. Zhou Y, LoBello R, Chunsheng C, Crane N, Poshni F, Porter WW, Cain YT, Measurement of an Amorphous Form in a Pharmaceutical Drug Product using FT-Raman Spectroscopy, Amer. Pharm. Rev, 2010; 34-41.
37. International Conference on Harmonization (ICH) Q8 (R2), Pharmaceutical Development. Aug 2009.
38. International Conference on Harmonization (ICH) Q9, Quality Risk Management, Nov 2005.
39. International Conference on Harmonization (ICH) Q11, Development and Manufacture of Drug Substances Draft Guideline, May 2011.
40. Cogdill RP, Anderson CA, Drennen JK, Using NIR Spectroscopy as an Integrated PAT Tool, Spectroscopy, 19(12), 2004, 104-109.
41. Alcala M, Leo J, Ropero J, Blanco M, Romanach RJ, Analysis of low content drug tablets by transmission near infrared spectroscopy: selection of calibration ranges according to multivariate detection and quantitation limits of PLS models, J. Pharm. Sci, 2008; 97: 5318–5327.

42. Johansson J, Sparen A, Svensson O, Folestad S, Claybourn M, Quantitative transmission Raman spectroscopy of pharmaceutical tablets and capsules, Appl. Spec, 2007; 61: 1211-1218.
43. Eliasson C, Macleod NA, Jayes LC, . Clarke FC, Hammond SV, Smith MR, Matousek P, Non-invasive quantitative assessment of the content of pharmaceutical capsules using transmission Raman spectroscopy, J. Pharm. and Biomed. Anal, 2008; 47(2): 221-229.
44. Blanco M, Bautista M, Alcala M, Preparing Calibration Sets for Use in Pharmaceutical Analysis by NIR Spectroscopy, J. Pharm. Sci., 2008; 97(3): 1236-1245.
45. Sonja SS, Howard WW,, Daniel RB, Elizabeth DS, Evans CL, Sciavolino ST, Hailey P, Aldridge PL, On-Line Monitoring of Powder Blend Homogeneity by Near-Infrared Spectroscopy, Anal. Chem., 1996; 68(3): 509- 513.
46. Igne B, Zacour BM, Zhenqi S, Talwar S, Anderson CA, Drennen JK, Online Monitoring of Pharmaceutical Materials Using Multiple NIR Sensors—Part I: Blend Homogeneity, J. Pharm. Innov, 2011; 6(1): 47-59.
47. Zhou GX, Zhihong G, Dorwart J, Izzo B, Kukura J, Bicker G, Wyvratt J, Determination and Differention of Surface and Bound Water in Drug Substances by Near Infrared Spectroscopy, J. Pharm Sci, 2003; 92(5): 1058-1065.
48. Corredor CC, Dongsheng Bu, Douglas Both, Comparison of near infrared and microwave resonance sensors for at-line moisture determination in powders and tablets, Analytica Chimica Acta, 2011; 696: 84–93.
49. Ward HW, Frank ES, On-line determination and control of the water content in a continuous conversion reactor using NIR spectroscopy, Anal. Chim. Acta., 2007; 595(1-2): 319-22.
50. John F. MacGregor, Mark J. Bruwer. Framework for the development of design and control spaces. J. Pharm. Innov., 2008; 3: 15–22.
51. Muteki K, Swaminathan V, Sekulic SS, Reid GL, De-risking Pharmaceutical Tablet Manufacture Through Process Understanding, Latent Variable Modeling, and Optimization Technologies, AAPS Pharm Sci Tech, 2011; 12(4): 1324-1334.
52. Muteki K, Yamamoto K, Reid GL, Krishnan M, De-risking Scale-up of a High Shear Wet Granulation Process Using Latent Variable Modeling and Near Infrared Spectroscopy, J. Pharm. Innov, 2011; 6(3): 142-156.
53. General Principles of Software Validation: Final Guidance for Industry and FDA Staff, US Food and Drug Administration (CDER &CBER), July 2013.

54. Good Automated Manufacturing Practice (GAMP) Guide 4.0,International Society for Pharmaceutical Engineering (ISPE), July 2013.
55. Junker BH, Wang HY, Biotechnol Bioeng , Bioprocess monitoring and computer control: key roots of the current PAT initiative, 2006; 95(2): 226– 261.
56. Medendorp J, Lodder RA, Acoustic-resonance Spectrometry as a Process Analytical Technology for the Quantification of Active Pharmaceutical Ingredient in Semi-solids AAPS Pharm Sci Tech, 2006; 7(1): E1–E9.
57. Li W, Bagnol L, Berman M, Chiarella R, Gerber M, Applications of NIR in early stage formulation development. Part II. Content uniformity evaluation of low dose tablets by principal component analysis, International Journal of Pharmaceutics, 2009; 380: 49–54.
58. Mantanus J, Ziemons E, Lebrun P, Rozet E, Klinkenberg R, Streel B, Eyrard B, Hubert P, Talanta doi:10.1016/j. Talanta, 2009; 10.019
59. Ghorab MK, Chatlapalli R, Hasan S, Nagi A , Application of thermal effusivity as a process analytical technology tool for monitoring and control of the roller compaction process, AAPS Pharm Sci Tech, 2007; 8(1): E155–E161.
60. Akseli I, Cetinkaya C, Mechanical and geometric property characterization of dry-coated tablets with contact ultrasonic techniques, International Journal of Pharmaceutics, 2010; 392: 148–155.
61. Benedetti C, Abatzoglou N, Simard JS, McDermott L, Leonard G, Cartilier L, Cohesive, multicomponent, dense powder flow characterization by NIR, International Journal of Pharmaceutics, 2007; 336: 292–301.
62. Ho L, Muller R, Romer M, Gordon KC, Heinamaki J, Kleinebudde P, Pepper M, Rades T, Shen YC, Strachan CJ, Taday PF, Zeitler JA, The analysis of sustained-release tablet film coats using terahertz pulsed imaging, Journal of Controlled Release, 2007;119: 253– 261.
63. Sun C, Zang H, Liu X, Dong Q, Li L, Wang F, Sui L, Determination of potency of heparin active pharmaceutical ingredient by near infrared reflectance spectroscopy, 2010; 51(5): 1060-3.
64. Rosa SS, Barata PA, Martins JM, Menezes JC, Talanta, Development and validation of a method for active drug identification and content determination of ranitidine in pharmaceutical products using near-infrared reflectance spectroscopy: a parametric release approach, 2008; 75(3): 725–733.

65. Paris I, Janoly DA, Paci A, Mercier L, Bourget P, Brion F, Chaminade P, Rieutord A, Avances en la aplicación de la sectroscopiea NIR, J Pharm Biomed Anal, 2006; 41: 1171–1178.
66. Onge L, Kwong E, Sabsabi M, Vadas EB, Rapid analysis of liquid formulations containing sodium chloride using laser-induced breakdown spectroscopy, J Pharm Biomed Anal, 2004; 36: 277–284.
67. Lopez AR, Garcia EA, Andrade JM, Avila G, Rosas JA, Hipolito EA, Vib Spectrosc, 2009; 51: 255–262.
68. Tabasi SH, Moolchandani V, Fahmy R, Hoag SW, s Sustained release dosage forms dissolution behavior prediction: a study of matrix tablets using NIR spectroscopy. Int J Pharm, 2009; 382: 1–6.