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Review Article

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A Review on Process Analytical Technology (PAT) & its Application

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Abstract

Process Analytical Technologies (PAT) describes 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. The PAT initiative focuses on building quality into the product and manufacturing processes, as well as continuous process improvement. It is well known that pharmaceutical production involves the manufacture of the finished product, followed by laboratory analysis to verify quality. The disadvantages associated with this approach are continual process optimization, recurring manufacturing difficulties, and the possibility of failed batches. This article provides an overview of Process Analytical Technology and its application to the pharmaceutical industry. It, however, is a wide-ranging subject, which is expanding rapidly. 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. On the top of that PAT applications, increase detailed knowledge of processes, leading to increased robustness and greater processing opportunities. Emphasis is placed on chemometrics, which is the use of mathematical and statistical models to extract and interpret chemical data.

Keywords: Process Analytical Technology, ICHQ10, Process analyzers, cost control, chemometrics

Contents

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1. Introduction

Process analytical technology (PAT) is one of the objectives contained in the Initiative for Pharmaceutical cGMPs for the 21st Century published by the Food and Drug Administration (FDA) 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. According to the FDA's guideline, PAT can be defined as a

system for designing, analyzing, and controlling pharmaceutical Manufacturing through the measurement of critical quality and performance parameters.

The measurements performed on raw and in process materials or process Parameters are intended to enhance final product quality. Process analytical technology encourages technological innovation, specifically the adoption of new analytical techniques by the pharmaceutical industry designed to improve the understanding and control of manufacturing processes. Both the FDA and industry experts expect benefits over conventional manufacturing practices: higher final product quality, increased production efficiency, decreased operating Costs, better process capacity, and fewer rejects. Correspondingly, fundamental Changes are also expected within the regulatory framework. The future of pharmaceutical production will require innovative technological approaches and more science - based processes. PAT will boost collaboration between research and development (R & D) and manufacturing departments inside companies and increase overall efficiency. Approvals and inspections will increasingly focus on scientific and engineering principles. As a result, regulators will set higher expectations for new products from the outset.

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.[1]

2. Description

Reason for Motivation of Process Analytical Technology (PAT)

The FDA [2] noticed that nearly all recent drug developments lacked the possibility of enhancing and extending process capabilities toward newer or alternative technologies. More specifically, the FDA wanted to encourage drug manufacturers to achieve more innovation and improve risk management when releasing new medicines on the market. When a quality problem arises in present - day production, it is increasingly difficult to identify the root cause. Thorough understanding of process and product performance often comes up against knowledge barriers, whether due to the escalating Documentation burden, lack of time, or loss of expertise. The goal of PAT is to enhance process control and understanding so that procedures can be performed differently and more efficiently. The PAT initiative facilitates and encourages the Introduction of innovative approaches. It makes it possible to consider shifting from Validation to continuous verification. The next step is effective real - time release with continuous processing as an alternative to the conventional batch after batch scheme. 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. [3]

Time 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. 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. 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. 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. for example, 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. Control is possible before the risk of failure is increased. Such an approach is complementary to container wise identification of materials on delivery to a warehouse.

Basis for Process Analytical Technology

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).

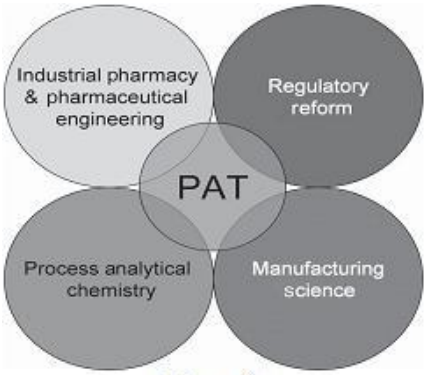


Figure 1

PAT Tools

PAT focuses on the principles of building quality into the product and process as well as continuous process improvement.

A few examples of PAT tools and strategies are as follows:

1. At-line, in-line, or on-line measurement of process quality and performance attributes using a variety of instrumentation and measurement strategies such as near-infrared (NIR), vibrational, acoustical, and X-ray spectroscopy
2. Chemometric approaches such as multivariate statistical and pattern recognition methods.
3. Real-time data and information management systems for process control [4].

The PAT initiative is part of a larger FDA initiative called "Pharmaceutical CGMPs for the 21st Century: A Risk-Based Approach"[5, 6]. The agency seeks to improve the regulation of pharmaceutical manufacturing using a science- and risk-based approach to product-quality regulation while incorporating an integrated quality-systems approach.

Types of Process Measurement

Nondestructive measurements that contain information related to biological, physical, and chemical attributes of the materials being processed. These measurements can be:

[1] Off-line testing: Transport of sample from the chemical plant to a laboratory for measurement.

[2] On-line testing: Measurement where the sample is diverted from the manufacturing process, and may be returned to the process stream.

[3] At-line testing: Measurement where the sample is removed, isolated from, and analyzed in close proximity to the process stream.

[4] In-line testing: Measurement where the sample is not removed from the process stream and can be invasive or noninvasive

Off-Line Testing

In this case laboratory is separated from the production plant. As a result, sample are Transported 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.[(7)]

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.[(8)]

At-Line Testing

This is the movement of process dedicated testing equipment is brought to the production line to provide rapid results, is more efficient, but still requires trained personnel. One advantage is elimination of the transfer of samples involving time delays. The instrumentation requirements will differ from those of laboratory instrumentation. Along with traditional tests such as dissolution, assay, friability, hardness, and thickness, this could also include accelerated dissolution rate analysis, and NIR tablet analyzers.

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. 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 a means to add on or in-line analysis at the production level.

Table 1: Process Analysis Differ from Laboratory Measurement **[9, 10, 11]**

S.No	Laboratory Easurment	Process Analytical Measurement
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.

PAT Applications:

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

Categories to be Benefited	PAT Benefit
Reduced operating cost	Increased operating efficiencies, Improved cycle time, Decreased operating costs, Continuous processing, Real- Time monitoring, Feed-Back controls & Results, Inventory reduction, Increased capacity utilization, Attain production schedule, Reduced reprocessing expenses.
Quality Improvements	Increased quality, Increased regulatory compliance, Increased product uniformity, Process finger printing, Increased process understanding, Quality designed into process, use of scientific, risk- based approach, Recall prevention, No sampling requirements, Critical process control provided, Rapid identification of counterfeit substances.
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
Positive research & discovery impact	Reduced product development life cycle/ time to market.
Increased occupational safety	Decreased occupation exposure to toxic substances

Drivers in Process Analytical Technology (PAT)

The goal of the PAT-oriented approach is to continue to ensure patient health by the availability of safe, effective, and affordable medicines.

Regulatory Drivers

Assurance of affordable, safe, and effective drugs for all citizens ensuring a high quality of drugs

Facilitating manufacturing process innovations

Drug quality depends more on best development, production, storage, and distribution strategies than on expanded quality testing. With PAT, there will be a shift from lab-based end-product quality testing to better formulation and process design leading potentially to more in-line, on-line, or at-line testing. Innovation transfer to routine production ensuring “state of- the-art” manufacturing processes should be accelerated by regulatory authorities. Potentially there should be fewer post approval regulatory submissions supporting process improvements.

Regulatory Benefits:

1	Time to approval	reducing time for administration of Chemistry, Manufacturing, and Controls (CMC)/dossiers for new drugs as well as for submission changes of approved drugs.
2	Improved process understanding	Process understanding is the basis for process control and assured end product quality.
3	Reduced inspection frequency	It can be reduced if the process Understanding meets the desired level.

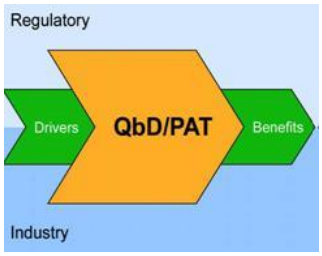
Additional Industry Drivers:

1	Reduced manufacturing costs	costs of manufacturing or QA could be decreased by increasing productivity and greater availability of production equipment.
2	More flexible & safer manufacturing processes	bridging the gap between the R&D, Manufacturing, QA, QC , and IT departments
3	Real-time release	help to reduce the time in warehouses of raw materials, final and intermediate products, or bulk (work in progress)

Industry Benefits

- Use of "state-of-the-art" technologies in manufacturing
- guaranteed quality level ("unit-to-unit")
- reduced documentation
- Risk mitigation
- Real-time data acquisition and integration
- Knowledge management

Knowledge transfer from other industries (e.g., IT, food, automotive, electronics) is reasonable and useful. Reduced personnel placement, less Out-of-Specification (OOS) batches, reduced lead time, cleaning, set-up, or maintenance time, will lead to an increased Return on Investment.



QbD: A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding based on sound science and quality risk management[(12)].

A Change in Strategy

The traditional approach to regulating quality in pharmaceutical manufacturing involved a laboratory analysis to verify quality after manufacturing the finished product. The disadvantages of this approach are continual process optimization, high levels of rejected product and limited adoption of new technologies The key to the success of PAT is applying the process monitoring tools needed to analyze each of the critical product attributes. One of the prominent techniques of PAT is online monitoring, which means it's not only recording information, but it's also closing the loop and making adjustments to the process as the product is being manufactured & help to reduce lifecycle costs while assisting manufacturers with ever- changing compliance regulations.

PAT Implications on Organization and Process

Implications on the Organization

Implications on Personnel

Demand on qualification and/or skills of employees may change:

1. PAT may have an impact on qualification profiles in respect to scientific data analysis, statistics, process control, etc. Similar to implementing Six Sigma, implementing a PAT program may require dedicated training

2. On methods and tools, including project management and statistics. (Probably at all levels of the company comparable with the Six Sigma training structure – master black belts, black belts, green belts, white belts?)

Structural change within the organization:

1. There may be a need for the implementation of a new department or restructuring of departments to deal with the new demands.
2. Interactions and collaborations between departments and functions may need to be increased (e.g., quality, regulatory, development, commercial production). Contact with regulatory authorities may need to be increased
3. 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).
4. Depending on the structure of the company, employees working for a PAT project could remain members of different departments or be integrated in a separate. PAT team or department.
5. Depending on the PAT approach (holistic or more specialized), an interdisciplinary project team with members from QA, R&D, Engineering, QC, IT, Manufacturing may be useful.

Implications on Management

1. The management has to be committed to PAT to deal with the early phase of PAT, which could mean more investment. However, in later phases, when processes are more efficient due to PAT elements, companies will be able to maintain quality at lower costs, and will be prepared for any future regulatory demands from agencies and thus be on top of the trend.

Risks concerning the company:

a. If PAT is ignored, there may be a risk of being left behind in the industry (competitive disadvantage) as well as a risk of image or business loss due to lower operational efficiency in sustaining reproducible product quality.
b. Regular review of benchmarks to stay on top of the project.

Outsourcing:

a. Communication: Communication between all kinds of different partners (e.g., departments departments,
b. Vendor Company, company agencies, etc.) may need to be intensified.

Implications on the QA Approach

a. **Audits**: Comparison between real design space and documented design space will be in the focus of an audit.
b. Validation: Validation will be demonstrated by continuous measurement of critical-to-quality parameters in real/near real time instead of the traditional three batch validation.
c. **Documentation:** The four areas of Process Understanding linked to Risk Management, QA/QC, Technology, and IT

PAT Impact on the Process

Impact on Process Understanding

Development of process models: The analysis of the process should define which parts have some flexibility and which are very rigorous. In order to define system/process boundaries, (re-)structuring of complex processes may be helpful.

1. Situation analysis is the evaluation of historical data for marketed products (from specification results, corrective actions).
2. Impact analysis is the identification and evaluation of process steps, sources of variation, and the variables that are critical to quality.
3. Critical process parameters need to be identified using appropriate techniques (e.g., FMEA, statistical analysis, risk analysis, and root cause analysis).
4. Monitoring/controlling of the process through definition and implementation of relevant measurements. This is necessary to obtain data which can be reviewed for better process/product understanding and control.
5. Verification of the control cycle is necessary to understand the impact of process parameters on process/product quality.

Impact on Production-Related QA/QC

Specifications

Quality control testing will evolve from testing against a discrete specification (pass/fail) to real-time comparison of process/product signatures against a reference. This reference will be a specification which will look totally different in a PAT approach as the process set values are flexible and based on a control strategy incorporating the design space.

QC testing

a. Parametric release and in-line control could have an impact on QC headcount and work.

b. There may be a necessity for additional verification of parameters and definition of prerequisites for parametric release.
c. In order to recognize a slow deviation from expected requirements (e.g., raw materials, wear of materials, etc.), additional controls may be needed.

Continuous improvement

Under PAT, manufacturing processes are monitored and controlled on-line, which – as opposed to a static process validation – leads to continuous process improvements. A continuous improvement and control of design space will be increasingly important

Equipment validation, including the control cycle

In contrast to the common validation approach, where testing the functionality of the immediate equipment is sufficient; with PAT, the complete control cycle of the equipment is included.

Impact on Process Technology

Continuous production: New equipment, design and . After the identification of critical process parameters space may be needed to enhance data acquisition and process understanding. Better knowledge of the process could lead to continuous production and faster release.

Impact on PAT-Related Data Management/IT

New software/tools and new methods:

New equipment, tools (e.g., SOA, XML), New methods (e.g., MVDA, DoE, process modelling) including knowledge base maintenance or applications may be needed to enhance data acquisition and analysis. Infrastructure, databases, and software should enable easy data mining. There will be increasing scrutiny on software validation at regulatory audits and The requirement for complete validation of software may start even earlier during research

Steps to Implementation

The implementation of a PAT program requires identifying the relevant technologies that can be applied and the creation of an integrated data management infrastructure capable of handling the volume of data to be recorded. It also requires advanced automation, visualization and analysis tools to manage the continuous identification and prediction stages in the process. Aanalytical in PAT is viewed broadly to include chemical, physical, microbiological, mathematical, systemic, control and risk analysis conducted in an integrated manner. A PIA report identifies possible productivity improvement opportunities such as:

a. Identification of best practices
b. Reusable engineering components
c. Cost reduction
d. Key performance indicators (KPIs)

Factors Limiting Implementation of PAT

1	Real & Perceived Technological Barriers	near infrared spectroscopy (NIR) has been used industrially for decades there has been hesitance to accept and trust “new” process analytical measurement technologies as equivalent or superior to traditional methods.
2	Lack of Economic Incentive	there is not sufficient financial return from investment in process analytics or manufacturing technology Upgrades to justify spending

Importance of PAT:

Cost control, resulting partly through more 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.

Approach to the PAT and Awareness Project with Case Studies

The basis for the PAT awareness document was the evaluation of 11 PAT case studies. The identification and evaluation of benchmarking parameters concerning PAT applications is important for various aspects:

a. To raise acceptance in the management
b. To proof the maturity of projects
c. For monitoring project progress

The following categories have been considered for this assessment:

1	Quality	OOS , better analysis methods, Reduction of complaints and recalls
2	Process	inclusion of new process automation technologies including of sensors, analytical devices
3	Risk	positive state-of-the-art methodology for risk detection and minimization (Risk assessment)
4	Cost	fewer rejected batches, fewer deviations, increased yield with higher Overall Equipment Effectiveness (OEE), fewer consumables, less waste, and fewer reworks.
5	Personnel	no reduction in personnel, slight increase in personnel safety
6	Tools	Applied analytical methods: NIR, MIR, Raman, laser diffraction, mass spectroscopy, accelerated dissolution testing, etc. Applied statistical methods: MVDA, DMAIC, etc
7	Time	Higher utilization of resources
8	Validation	more effort has to be put into facility, equipment, and software validation during PAT implementation.
9	Organization	increase the interdisciplinary communication between departments
10	Regulatory	The frequency of scientific-based contacts and communications with regulatory bodies

Table 2: PAT application in chemical industry [13,14]

Application	**Process ANALYZER**	**Observation**
Analysis of organic content of waste water	NMR Spectroscopy	Less time & Cost effective method
Raw material identification and quality control	Near infrared (NIR) Spectroscopy	Fast & cost effective method
Simultaneous monitoring of solute concentration and Polymorphic state of crystal	Raman spectroscopy &Attenuated total reflectance(ATR) and FTIR	Know how the rate of addition of reactant affects the Polymorphic state of crystal
Catalysis reaction involving conversion of Acetone to Methyl isobutyl ketone(MIBK)	In-line NIR	Affects productivity, selectivity, and yield of MIBK

Table 3: PAT application in Pharmaceutical industry [15, 16, 17]

PAT	**Process**	**Attribute analyzed**	**on/in/off-line**
NIR-ST	compression	Quantification of active ingredient	Off-line
Temperature sensor & increase	Granulation	Granulation end point	In-line
NIR-SR	Raw material	Identification	Off-line
NIR-SR	Packing line	Identification	On-line
NIR-SR	granulation	wet granulation end point	On-line
NIR-SR	Packing component identification	Identification of blister PVC-films	Off-line
NIR-SR	Compression - tablets & capsules	Content uniformity & assay	Off-line
NIR-SR	powder	moister content	Off-line
NIR-SR	High shear granulation	Particle size & shape	In line
NIR-SR	Pharmaceutical salt formation process	End point monitoring	In line
NIR-SR	Compression	Analysis of API in tablets	Off-line

NIR spectroscopy - Transmission = NIR-ST
NIR spectroscopy reflectance = NIR-SR

Process Analyzers:
Process analyzers [18] measure the physical, chemical and biological properties of materials. They collect both quantitative data and qualitative data. Data collection can be nondestructive, require minimal sample preparation, and have rapid or real time response when compared to traditional methods. Data integrity is necessary to ensure compliance with the U.S. FDA 21 CFR Part 11 which requires specific controls with respect to electronic signatures, security, and audit trail functionality. On-line and in-line process analyzers have the greatest potential to reduce operating costs and improve quality; both minimize sample requirements and sample handling compared to their at-line and off-line counterparts. Clevett indicated that 80% to 90% of errors associated with analysis were associated with sample handling, either directly or indirectly. On-line & in-line process analyzers reduce sample retest and cycle times.

Process Analytical Chemistry (PAC) and in/at/on-line monitoring
PAC is the technique of "gathering analytical information in real time at the point of manufacture (Hailey et al)" places an emphasis on the process rather than the final product," including "an understanding of the relationship between final product specification [sic] and the critical variables during the manufacturing process [19, 20]. The following is a partial list of the various sensors and instrumentation recently discussed at the 2003 Arden House Conference either in-use or currently being evaluated for feasible use for production monitoring:

a. NIR spectroscopy for moisture determination
b. X-ray spectroscopy
c. Radio frequency for moisture determination
d. Microwaves for moisture determination
e. RAMAN spectroscopy, with vibrational spectroscopy being

The most common. RAMAN complements IR spectroscopy and is used for raw-material identification, polymorph differentiation, and reaction monitoring.

a. Fluorescence for water quality
b. On-line measurement of color
c. X-ray fluorescence for the detection of inorganic materials
d. photoacoustic spectroscopy.

Because most of these technologies are extremely sophisticated, one must realize that the key emphasis of PAT is not so much how to collect the data or what kind of instrumentation should be used, but rather what data should be collected, what is done with these data, and what associated conclusions are reached. Therefore, a complete and thorough understanding of the manufacturing process is paramount.

Near Infrared [21, 22]
Pharmaceutical formulation, could be robust and consistent, any tablet or capsule produced anywhere in the world must have the same therapeutic characteristics. A basic problem in pharmaceutical manufacturing is that seemingly simple formulations with identical ingredients can exhibit radically different performance depending upon how the ingredients are blended together. Tthe most significant factor in determining the quality of a formulated product, is the structure of the matrix that evolves during this manufacturing process, when it is time to assess the quality of our products, we invariably destroy the matrix by dissolving the sample in a solvent. All the information on the physical state of the ingredients and how they relate to each other is then effectively lost. Near infrared (NIR) imaging is an exciting new technology capable of providing insight into the structure and function of modern solid dosage forms. It has gained recent recognition as a means to add on or in-line analysis at the production level and results of these evaluations compare favorably to those of traditional methods such as sieve analysis, digital microscopy and particle size instrumentation. The near-infrared light does not destroy or react with samples and is able to penetrate into and through solid samples. Monitoring particle size and control of the manufacturing process prevents over-processing of the product. The shape and spatial distribution of particles influence physical properties such as powder flow and filterability. Clarke used NIR microscopy off-line to determine spatial distribution and cluster size of ingredients in granulation and compressed pharmaceutical products.While NIR has gotten most of the attention, PAT is not limited to NIR but can include many other forms of monitoring, such as Raman, Mid-IR, acoustic emission signals, and other imaging techniques.

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

of drug and excipient were tested and, according to these results, the Raman is potentially a good analysis technique, which offers obvious benefits compared to other presently commonly used techniques in pharmaceutical research. Raman spectroscopy allows high-speed analysis of a large amount of samples, due to minimized sample preparation and short measuring times. The high selectivity and sensitivity of Raman spectroscopy enables the use of simple calibration methods in many cases. Furthermore, the Raman spectrometer can be easily installed into the process environment because the Raman signal can be measured through the glass window or plastic packages.

CCD camera:

Watano et al. Assessed particle size in a high share granulator in-line through the use of an image probe. The image probe was combined with a fuzzy logic control system to control granulation growth in the high shear granulator, preventing excessive granule growth. The system was capable of accurately and reliably producing granules that met specifications, independent of starting materials and operating conditions. Assessed particle size growth (Laitinen et al) in a fluidized-bed granulation process using a monochromatic CCD camera. At-line analysis of granulation samples growth and granulation end point for the fluidized bed granulation process. The conclusion was that the imaging approach used provided rapid evaluation of granule particle size.

X-ray Diffraction:

An XRD-pattern is a direct result of the crystal structures, which are present in the pharmaceutical under study. For multi-component formulations, the actual percentages of the active ingredients in the final dosage form can be accurately analysed in situ, along with the percentage of anyamorphous packing ingredients used.XRD is the key technique for solid-state drug analysis, benefiting all stages of drug development, testing and production. On-line application of x-ray powder diffraction was evaluated by Davis et al. for use in monitoring the transformation of the flufenamic acid. The results of this evaluation suggest that X-ray powder diffraction may be used as an on-line process analyzer to monitor granulation process and parameters such as granulation end time.

FT-IR process Analyzer:

Process analyzers have been evaluated for API synthesis. Watson et al recommended the use of the in-line FT-IR process analyzer to monitor and control the synthesis process since in this process ensures API quality and predicted the need for batch reprocessing. Lin et al demonstrated the ability to real-time monitor a pharmaceutical salt formation process with FT-IR coupled with an ATR probe, a task which cannot be accomplished with traditional analytical instrumentation. Such as titration and HPLC. FT-IR ATR permitted differentiation between mono and bi-salts allowing for real-time determination of the synthesis endpoint. Other benefits were improved quality monitoring, higher yields, and end of method transfer between laboratories and FT-IR instruments, all of which contribute to improved efficiency.

Laser-induced fluorescence or LED induced fluorescence (LIF):

It is a spectroscopic method used for studying structure of molecules, detection of selective species and flow visualization and measurements. This fluorescent light is typically recorded with a photomultiplier tube (PMT) or Filtered Photodiodes. An advantage over absorption spectroscopy is that it is possible to get two-and three-dimensional images since fluorescence takes place in all directions (i.e. the fluorescence signal is usually isotropic). The signal-to-noise ratio of the fluorescence signal is very high, providing a good sensitivity to the process. LIF is useful in the study of the electronic structure of molecules and their interactions. LIF technology is selective for fluorescent materials with in a drug formulation. LIF measures the emission wave length as a result of wave length excitation. LIF technology is a nondestructive. PAT tool for the analysis of powder mixing kinetics, blend homogeneity and tablet active ingredient content. Lai and Cooney proposed that LIF would be especially useful within the pharmaceutical industry because 60% of the two hundred main active ingredients fluoresce. Benefits of on-line LIF analysis in blending include real-time blend kinetic results and reductions in errors due to thief sampling.

Chemometrics [23]

To fully understand PAT, one must first understand the science behind manufacturing processes, including how these processes operate, their limitations, and their expected outcomes. This art is heavily dependent on the use of different kinds of mathematical models" and that it was important to have knowledge in statistics, numerical analysis, and applied mathematics, including the challenge to structure the chemical problem to a form that can be expressed in a mathematical relation (Umea, Sweden, 1974). How do we get chemically relevant information out of measured chemical data; how do we represent and display this information; and, how do we get such information into data (Professor Wold, 1994). Chemometrics is the science of relating measurements made on a chemical system to the state of the system via application of mathematical or statistical methods" [24]. Similarly, Hardy noted that data are "raw information, both qualitative and quantitative" [25]. Chemometrics [26] is complex and requires the use of computers and software to perform the necessary computations. These techniques reduce large amounts of data into a few recognizable components without any loss of data. Two chemometric techniques that have been found to be useful are Principal Component Analysis (PCA) and Partial Least Squares Regression (PLS). These techniques are recognized for their ability to eliminate noise, identify latent variables, and extrapolate missing data. PCA is a technique of creating data models of previously produced and tested batches to verify similarity to newly

created batches. One advantage this technique has over the commonly used f2 metric is that batches are now compared to a substantial compilation of batches included in a validated model. Trends could potentially be identified earlier than with an f2 comparison. This could help improvement of process consistency after scale up and post approval changes. Another advantage of PCA is that it can handle the large amount of data produced by dissolution fiber optic (Dis-FO) techniques without the need to reduce data points. PLS is used to correlate data, such as finished product dissolution results, to raw material, process parameters, and in-line readings. Variables which affect the dissolution rate can be better understood and monitored. The effect of scale ups and post approval changes can be quantified. Critical parameters can be controlled, thereby creating high quality drug product, less level/stage 2 testing, and minimal product failure. When out of specification results do occur, drug products can be better investigated through the use of PLS to determine which underlying variables contributed to the failing drug product.

Multiway principle component analysis (MPCA):

An analog of PCA is what is known as *multiway PCA*, which is "equivalent to performing PCA on a very large two-dimensional matrix formed by unfolding the three-way array *X* into one of six possible ways, only three of which are mathematically unique".only three of which are mathematically unique".

Multiway partial least squares (MPLS):

Nomikos and MacGregor observed that MPCA using statistical process-control charts "only makes use of the process variable trajectory measurements (*X*) taken throughout the duration of the batch" [27]. Other statistical tools. Two other statistical tools that may be useful in PAT efforts are

1. Capability studies: It measure the ability of the process to consistently meet specifications by evaluating select process
2. Outputs and calculating the average and ranges over a specified time on control charts. From these studies, capability indicies Cp (used to evaluate the variation) and Cpk (used to evaluate the centering of the process) are calculated.
3. design of experiments: These are experiments that involve changing one or more of the process inputs and measuring the results to one or more of the process outputs [28].

Rapid microbiology test methods [29]

Two problems or risks associated with the development of rapid microbiology methods; namely,

a. Validation of test methods may not yield results equal to those for traditional test methods
b. Acceptance by regulators (e.g., FDA).
c. The group also categorized microbial determinations as follows:
d. Qualitative methods (presence or absence of microbes; e.g., sterility testing)
e. Quantitative methods (enumeration of microorganisms present; e.g., microbial limits tests)
f. Microbial identification.

FDA did concede that rapid microbiology test methods are an important part of the PAT initiative The general guidance document on PAT would not specify details about rapid microbiology methods but would rather cover them in a general sense to encourage their use.

3. Conclusion

The use of process analytical technology can provide huge benefits to those who choose to use the technology as in the pharmaceutical industry by increasing product quality while delivering superior asset utilization and financial value. 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. PAT provides better knowledge of raw materials by characterizing it both physically and chemically understanding of manufacturing parameters all of which is having the impact on the finished product quality. This will result in a more robust process, better product, more uniform dissolution results, better process control and huge time saving which ultimately result in a good cost savings along with creation of a unique brand image for the organization. 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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