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Process Analytical Technology-Recent Advances

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Abstract: Process analytical technologies had been applied to manufacturing processes for decades. Recently, the US Food and Drug Administration (FDA) had re-defined the phrase and implemented into an initiative focusing on improving the several aspects of pharmaceutical industry; European agency for the evaluation of Medicinal products (EMEA) has formed a PAT team in 2003.
The PAT initiative was initially intended for traditional pharmaceutical manufacturers, but the FDA's PAT guidance clearly states that it applies to all manufacturers of human and veterinary drug products, as well as biologics regulated by the center for veterinary medicine (CVM) and FDA's Center for Drug Evaluation and Research (CDER).
Basically, PAT involves testing the quality of the finished drug product, to build the quality into products by testing at several intermediate steps. In this report, the impact and potential effects of PAT on the biotechnological production of pharmaceuticals is assessed and it has been focused on what PAT means in practice for the biotechnological manufacture of pharmaceuticals. It specifically requires quantifiable, casual and predictive relationships, established amongst the initiative for a period of innovation, efficiency and expansion for the biopharmaceutical industry.

Keywords: Analytical tool; Quality; Safety; Efficiency; Validation.

Introduction:

PAT can be defined as a system for designing, analyzing, and controlling pharmaceutical manufacturing through timely quality measurements and performance attributes of materials and processes. PAT is real-time testing and adjustment based on the complete understanding of how the components and related processes affect the final product. It includes chemical, physical, microbiological and mathematical risk analysis conducted in appropriate manner. [1] The fundamental principle of the PAT includes that quality cannot be tested, but is instead built into the medicinal product by design. A high degree of repeatability and efficiency can be achieved by actively managing the processes and quality assurance becomes continuous and real time activity. [1] [2] [3]

Benefits and Challenges:

Profits in quality, safety and efficiency mainly depend on the process and the product, and are likely to come from: [4]

- Reducing production cycle times by using in and at-line measurements and controls.
- Preventing rejects and re-processing.
- Real time release of product
- Improving operator safety and reducing human errors by increasing automation.

- Improving energy, material use and increasing capacity.
- Facilitating continuous processing to improve efficiency.

For example, in case of small-scale equipment (to eliminate certain scale up issues) [4]

- Decrease in cycle times
- Lowering costs
- Batch to batch consistency and increased efficiency
- Process fingerprinting (signature) that would be useful for validation, scale up, and conforming acceptable handling of changes.
- Increase in process understanding and decrease in variability, rejects, and lot failures
- Continuous processing and the ability to adjust process on the basis of real-time monitoring data.

PAT TOOLS:

The PAT tools is shown in figure.1

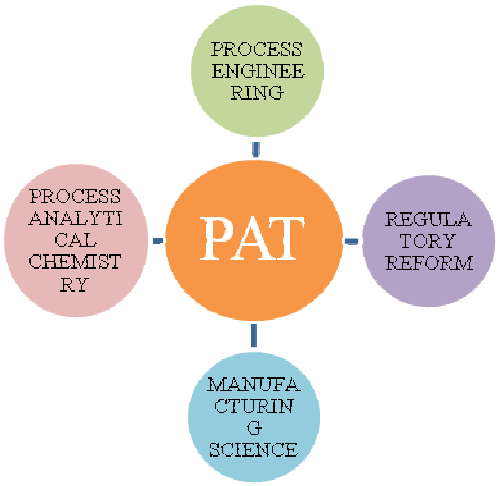

Fig.1 PAT tools [4]

The available PAT tools enable process understanding for scientific, risk managed pharmaceutical development, manufacture, and quality assurance and when these tools are used within a system, it provides effective and efficient means for acquiring the information and to facilitate process understanding, development of risk-mitigation strategies and continuous improvement. In the PAT framework, these tools can be categorized based on the following: [4].

- Multivariate tools for design, data acquisition and analysis
- Continuous improvement
- Management tools
- Process analyzers
- Process control tools

Combination of some, or all, these tools can be applicable to a single unit operation, or to an entire manufacturing process.

RECENT DEVELOPMENTS IN ANALYTICAL TECHNIQUES FOR CHARACTERIZATION OF ULTRA PURE MATERIALS:

The trace metal impurities of process materials and chemicals used in pharmaceutical industry are moving to increasingly lower levels, i.e. nano gram/gram and Pico gram/gram levels. A brief overview of the use of different analytical techniques in the analysis of trace metal impurities in ultrapure materials, such as, high-purity tellurium (7N), high purity quartz, high-purity copper (6N), and high purity water and mineral acids are used. In recent times mass spectrometric techniques such as ICP–MS, GD–MS and HR–ICP–MS with their high sensitivity and less interference effects were proved to be extremely useful in this field. A few examples of such application studies using these techniques are specified. The usefulness of other analytical techniques such as F–AAS, GF–AAS, XRF, ICP–AES and INAA was also described. Specific advantages of ICP–MS and HR–ICP–MS are high sensitivity, limited interference effects, element coverage and speed would make them powerful analytical tools for the characterization of ultrapure materials in future [5].

OTHER ANALYTICAL TECHNIQUES:

Instrumental neutron activation analysis (INAA) is also an established technique for the analysis of ultrapure materials. But requirements, such as, sample irradiation in a reactor and longer cooling times make this technique unsuitable for such industrial applications. Some of the elements like Cl and S can be conveniently determined by X-ray fluorescence spectrometry (XRF), as for many of the metals, the detection limits offered by XRF are not adequate. However, XRF was successfully utilized for the determination of impurities in surface layers of semiconductor materials. Detection limits of nano gram/gram and sub-nano gram/gram for several elements in different matrices are identified by inductively coupled plasma atomic emission spectrometry (ICP–AES). This is also a potential analytical tool for the analysis of ultrapure materials. Flame atomic absorption spectrometry (F–AAS) technique cannot detect and determine metals at ng/g levels in many cases. Though graphite furnace atomic absorption spectrometry (GF–AAS) possesses the required sensitivity, it is a slow technique and the analytical procedures in general are very cumbersome. Moreover, both F–AAS and GF–AAS are not multi-element techniques and cannot meet the throughput requirements. [6]

A PRACTICAL APPROACH TO PAT IMPLEMENTATION:

It has been estimated that the very best pharmaceutical manufacturing facilities could deliver one-off cash release of $76 billion. A further reduction to inventory levels is achieved in other manufacturing industries which would be a worth another $15 billion. Process analytical technology (PAT) is a key enabling technology to deliver these savings. [2]

The spectroscopic techniques such as Fourier transform infrared (FTIR), near infrared (NIR), mass spectroscopy (MS) and Raman together with chemo metric multivariate analysis tools and isolated quality assurance (QA) laboratories in the pharmaceutical industry are used. An on-line implementation process has been led by innovative groups of analysts and engineers who have recognized the potential of these techniques to improve understanding, it helps to resolve existing manufacturing problems and decrease the operating costs. These successes are notable in view of the conversation of the pharmaceutical industry as a whole, which acts as a barrier to innovation and change, particularly in the manufacturing domain. [7]

The on-line analysis and advanced process control in the pharmaceutical industry is currently undergoing rapid and radical change which highlight the support of FDA for continuous improvement in pharmaceutical manufacturing. [3]

The PAT concept is completely aligned with the FDA goal of a science and risk-based approach to current good manufacturing practices (cGMPS). As a direct consequence of the "cGMPs" for the 21st century" initiative, the pharmaceutical industry is experiencing from the regulator to address concerns around limited process understanding, process inefficiencies and continuous process improvement.[4] This appears will describe four key elements of a PAT implementation:

- Building the science-based knowledge base
- Process monitoring, control
- Validation of the PAT system
- Implementing PAT system-regulatory strategies building the science- based knowledge base:

The PAT guidance emphasizes the need to develop an understanding of the underlying scientific principles behind pharmaceutical manufacturing processes to determine the critical parameters to process and product quality. [4] The knowledge base provided by the PAT approach is valuable in three main ways:

- It is used for robust process and product design.
- It supports the flexible regulatory paths for innovative new approaches.
- It facilitates continuous learning throughout the product life cycle.

The design of experiments, capture and evaluation of analytical measurement data are essential parts. Knowledge is recommended at all stages of the product and process life cycle, beginning stage and extending through formulation, lab-scale production, scale-up, and pilot plant and full-scale manufacturing. [4]

In Research and Development, the PAT approach is concerned with the evaluation of information from research studies, stability and alternative dosage forms using new and conventional methods of analysis. Data collected from scale-up production batches and manufacturing batches is added to the knowledge base, it becomes useful during the product life cycle. Typically, this includes data on raw material attributes, process parameters, product quality attributes and environmental conditions, and the full range of variability. [8]

- Variations in raw material supplier manufacturing processes which causes impact on the chemical and physical attributes of the supplied materials.
- Time variations in manufacturing performance (e.g., between equipment maintenance events).
- Long-term equipment and degradation effects.
- Changes to equipment/analyzer hardware and software.
- Changes in the local environment (e.g., temperature and humidity).

PAT knowledge base is most benefit because it provides a means for the applicability of the multifactorial relationships between process and product attributes in different scenarios. [9]

Process monitoring and control:

Differences between current practice in pharmaceutical manufacturing and a PAT approach can be summarized as:

- Use of the novel analytical technologies
- The establishment of multifactorial relationships between materials, process and environmental conditions, and an understanding the changes of these relationships for product quality and process robustness.
- Use of the knowledge management tools.

The interaction between process and product is the basis for the design of the process monitoring, process control used in manufacturing.

It is important to realize that the process analyzers and PAT tools are used only for monitoring raw materials, process variables and process end-points do not constitute a PAT approach. PAT is an integrated approach in which the results are obtained from the real-time analysis of critical process. During manufacturing, process parameters are adjusted to produce the desired quality attributes at the process end-point. [10]

- Outcome of using a PAT approach in manufacturing is giving rise to change in the definition of quality decision criteria, and this includes acceptance criteria. The most important differences are:

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- Time-based end points towards the attainment of the defined quality attribute.
- Use of statistical principles to define acceptance criteria for product attributes based on the nature of the test and sample size.

Validation of a pat system:

FDA encourages the use of the PAT approach for **new drug applications (NDAs) and for approved products.** [3]

In case of approved products, data can be collected during manufacturing from process sensors and on-line analyzers, and evaluated using PAT tools. [12]

Validation plan for a PAT system typically include the validation of process analyzer hardware and software; software packages for data analysis; process control software; and IT systems for the management storage and backup of results. The PAT guidance would be the characteristic response of the system to a given stimulus.

Acoustic spectroscopy is the most familiar of these techniques. In such cases, comparison with the analytical method to a conventional method is often difficult. PAT guidance clearly indicates that test-to-test comparisons are not mandatory in such circumstances. The regulatory agency is prepared to review the use of techniques based on a comprehensive statistical and risk analysis but additional information such as a mechanistic explanation of casual links between the measurement results observed process variability. The predictive ability of the established correlation functions and multifactorial relationships is considered as a key indicator of process understanding in such cases [4].

Implementing a pat system-regulatory strategies:

PAT is a joint initiative of the center 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 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 science and risk-based approach to PAT. Additionally, a PAT review and inspection team has been established, includes reviewers, compliance officers and inspectors who have been trained and certified in the PAT approach. [4]

The PAT guidance emphasizes that implementation plans should be risk-based and the risk is regarded as being significantly lower when the process is well understood. This case is considered to be when.

- All critical sources of variables are identified and explained.
- Variability is managed by the process included.
- Product quality attributes can be accurately, reliably predicted.

CONCLUSION:

The aim of a PAT approach is to implement robust process that are flexible enough to accommodate a define level of variability in process materials (physical and chemical attributes) through adjustment of the process conditions.

A knowledge base provides the information for a science and risk-based approach to analytical method validation and process monitoring and control.

The efficiency and cost structure of the pharmaceutical industry in the use of advanced process control systems and on-line measurement

techniques for continuous QA. It can be speculated that without the voluntary movement toward improved process understanding and associated improvements in process efficiency and reductions in operating costs.

PAT APPROACH ON FLUID BED GRANULATION AND DRYING:

All pharmaceutical industries are now encouraged to use the latest scientific achievements to improve the quality and efficiency of the manufacturing. Protection of the patient is the ultimate goal for a pharmaceutical industry. Process analytical technologies (PAT) are utilized to ensure final product quality by designing, analyzing, and controlling manufacturing through timely measurements of materials and processes. [2, 3]

The pharmaceutical industry is advised to determine the design space initially during the product development through a repetitious process.

PAT principles and tools should be introduced during the development phase of a drug product by identifying and explaining all critical sources of variability, managing variability of the process, and predicting product quality. These tools may also identify the potential failure modes and quantify their effects on product quality. A process end-point is the achievement of the desired material attribute within the PAT framework. [4]

A choice for improving the processing properties of pharmaceutical powders, such as flow characteristics and tablet compaction is fluidized bed granulation.

Fluid bed granulation: It is a complex multi-factorial system. The effects of the critical parameters, critical quality attributes on the fluid bed process which includes moisture and particle size are very important to identify and control.

By implementing PAT principles and constructing the design space and monitoring the material behavior in a fluidized bed. Physical process measurements analyzed in an integrated manner are essential in process understanding. [2, 3]

The aim is to determine the correlations and relationships, and utilize the PAT and design space concepts for the fluid bed granulation and drying. Physical in-line measurements (i.e. Temperature, air flow rate) and various particle size determinations are used to increase the process understanding.

Design of fluidized bed systems:

The two most important methods to produce granules for pharmaceutical manufacturing in fluid bed granulation include mixing, wetting, drying and wet massing in a high shear mixer with a subsequent fluid bed drying. [10]

Mechanism:

The same principle by which air is drawn through the machine is used in case of fluid bed granulation and drying operation.

Generally the air flow is created by turbine fan suction located at the exhaust end. First air enters through the air handler, it is conditioned for the process and then it is drawn into the product processing area. The design of the gas distributor plate is essential for the material in a fluidizing process. Filter bags separate the product from the process air that is before the air exits into the atmosphere through an outlet air duct. [11]

A high shear mixer is placed in-line with a fluid bed processer, after the mixture is granulated in a high shear mixer, the dense material is transported to the fluid-bed dryer to dry and the transfer between them can be controlled by a single controller.

Objective:

The current objective of this approach is the air-

handling unit it produce air of consistent quality with the desired dew point throughout the year. In general, a high degree of control over the temperature and humidity of the process airstream results in fewer problems with batch-to-batch reproducibility.

In sophisticated systems the process air is heated, cooled, humidified, dehumidified and filtered as and it enters the fluid bed unit air handling system.

It has become common to monitor Moisture, particle size, polymorph changes and to control fluid bed process and fluid bed systems near infrared spectroscopy systems(NIRS) are utilized.

Fluidization behavior:

The mixing effect of a fluid bed process is generally good for particles between 50 and 2000µm. Fluidization behavior includes various interactions and interparticle forces. Other potential forces include liquid and solid brides. The interactions, in which the interparticle forces appear, are particle-particle, particle-chamber, and particle-gas interactions. [10][11]

Two approaches, minimum fluidization velocity U_{mf} and Geld art classification, are accepted and have the capability to predict and characterize the fluidization behavior of the solids. [11]

U_{mf} is used in quantifying one of the particle properties in a fluid bed. This term is referred to a stage, at a certain velocity and the elevating force of upward moving gas counter balances the weight of the bed. The changes observed are:

- At this point, the pressure drop across the bed equals the weight of the bed.
- The proper flow is required to maintain a complete homogenous bed of solids in which coarse or heavy particles will not segregate from the fluidized portion.
- After the bed is fluidized and the velocity of air is increased, the pressure drop across the bed stays constant but the height of the bed continues to increase.
- The design of distributor plate and the optimal pressure drop are the most important factors in fluid bed design in relation to fluidization.

Geld art classification consists of four groups that are characterized by the density difference between solid and gas, and the mean particle size of the solid phase that is from smallest to largest particle, they are as follows: C, A, B, D. [10][11]

Class C materials are cohesive and very fine powders. The inter particle forces in this group are stronger than those resulting from the gas flow and that leads to turbulent fluidization.

Class A materials fluidize easily and the beds of powders expand, before bubbling takes place. Fluid beds of 'A' powders are operated at gas velocities above the U_{mf} but below the minimum bubbling velocity (U_{mb}) are said to be particularly fluidized. Increase in gas velocity above U_{mf}, the bed further expands. The bed is fully particulately fluidized at some point, usually at high pressure.

Class B powders expand only a little before bubbling takes place and these solids fluidize easily. Bubbling occurs slightly above the minimum fluidization velocity. The bubbles are small and they coalesce as they rise through the bed.

Class D particles are large and the gas velocity on the dense phase is high, which results in poor mixing of these solids. An enormous amount of fluidized gas is needed to fluidize these solids. Bubbles in the bed coalesce rapidly and grow to large size.

The most important variable, of fluidization during the spraying phase, is the gas velocity that is the inlet airflow. The inter-particle forces required to cause de-fluidization are very small and, when

operated at velocities the bed collapses or 'freezes' due to over-wetting and uncontrollable granule growth. Under certain circumstances the static charges may result in freezing even when high air velocities are used.

Mechanical agitation in rotary fluid bed granulator enables the fluidization of materials with poor fluidization characteristics and increases the moisture content of the bed.

Process phenomena described by in-line particle size analyzer:

The in-line particle size analyzer rapidly detects the actual granule size changes and these changes are monitored in real time and analyzed.

Fluctuation was due to the fine material in the process, which returned to the fluidizing mass when filter bags were regularly shaken. This information can be used for formulation and process development. This process minimizes fine material during processing. [11]

Rapid increase in granule size could be observed, entrapment of fine particles in the filter bags causes a process deviation. As soon as the filter shaking mechanism was restored, the level of particle size results was monitored in a timely manner. Measured granule size and granule size fluctuation is decreased at the end of drying process in a few batches.

This relates to improper fluidization due to adhesion of fluidizing materials on the distributor plate. Pressure difference over the bed and inlet air flow rate measurements was measured. In addition, after the process the dry and fine material covered the chamber surfaces including distributor plate are noted, it is due to likely static electrical charges and vanderwaal forces contributed to this adhesion. The results of this study suggest that the fluid bed in-line application can be used to increase process understanding both during the process and by analyzing the data. [11][12]

CONCLUSIONS:

The automated fluid bed granulator equipped with versatile instrumentation system is used to study process related phenomena and to increase the understanding of the process of fluid bed granulation and drying.

Various analyze of different measurements revealed critical relationships and variation sources, which could be used for the basis for constructing a design space for process performance. This type of instrumentation system is an invaluable aid to gain more control for fluid bed processing and to obtain consistent and uniformity of granules for further processing. The heating effect of air related to humidity level and granulation batches in different parts of a granulator system were demonstrated. Temperature measurements at various positions were found to describe the progression of drying better than humidity measurements. The effect of granulation liquid feed (pulsing) on temperature of fluidizing mass was clearly seen and recorded and effect of inlet air humidity and granulation liquid feed on granule size were evaluated. Both increasing inlet air humidity and granulation feed increases the particle size.

There are four different failure modes which were identified and classified based on the fluidization parameter they are:

- Over fluidization,
- Risk of improper fluidization,
- Improper fluidization and collapsed bed.

It was possible to construct process for smooth fluidization, because we should follow the optimal granulation process.

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Various drying end-point criteria which is based on temperature and humidity measurements were compared with varying inlet air humidity, the commonly used ΔT temperature difference method give a more precise estimation of the drying end-point than the constant temperature criterion.

New developments were found into the correlation between moisture content and temperature of the fluidizing mass. The fluidization behavior greatly affects the end-point detection of drying. Therefore the use of the ΔT requires proper fluidization throughout the whole process.

The in-line particle size analyzer detects the actual granule size changes and these changes monitor both in real time and during analysis and more specifically afterwards. These phenomena includes a rapid increase in granule size which is related to the entrapment of fine particles in the filter bags and a decrease particle size due to the adhesion of fluidizing material on the distributor plate. Correlation between PLS analyzes reveals a significant relationships between various process parameters highlighting the particle size, moisture, and fluidization effects. Correlation with the in-line particle size was found between both the fluidization parameter and the pressure difference over the upper filters. The pressure difference over the granules and the temperature of the fluidizing mass express the moisture conditions of wet granulation.

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