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[Review article]

Process Analytical Technology

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ABSTRACT

The increasing demand for the better healthcare products has changed the pharmaceutical industry. In the recent years, the technologies producing the quality products have paved the way for good quality products. The introduction of new tools and technologies has provided an opportunity for the pharmaceutical producers to improve the quality standards of the product. PAT is one of the technologies in pharmaceutical production where they test out the quality of the raw materials, characterize them both physically and chemically, through at-line, in-line or on-line. PAT saves time and money required for testing and analyzing the products. The PAT paves the way for making good quality products thus satisfies the customers needs and build a good brand image for the organization. The two effective tools NIR and RAMAN spectroscopy are used in testing the quality of the products. This research essay delves the essentials of PAT and the usefulness of process analyzers in process monitoring. The effectiveness of the PAT tools and the advantages of NIR over RAMAN spectroscopy are clearly discussed.

Keywords: Process Analytical technology, Raman Spectroscopy, NIR (Near-Infrared Spectroscopy), PAT tools, Process Analyzers and Process Monitoring.

INTRODUCTION

Process Analytical Technology or PAT is a rebellion in the pharmaceutical industry initiated by the United States Food and Drug Administration to decrease the risk of producing a deprived quality product (US FDA[1]). The PAT recognizes and manages the manufacturing process, which is consistent with the current drug quality system. The framework of PAT helps to design and develop the processes that consistently ensure the predefined quality at the end of the manufacturing process. The procedures are consistent with the quality by design and reduce the risks to quality and improve the efficiency. PAT can be defined as the optimal application of PAC tools, feedback process control strategies, information management tools and product or process optimization strategies to manufacture drugs. It concentrates on the principles of maintaining quality in the product and process as well as continuous process improvement. PAT encourages continuous process manufacturing improvement like chemical, physical, microbiological, mathematical and risk analysis (US FDA[2]).

Near Infrared (NIR) and RAMAN spectroscopy are the tools which have been increasingly used for the measurements of critical process and product attributes during the process monitoring. These spectroscopic techniques allow fast and non-destructive measurements without any sample preparations. Both the techniques are molecular vibration spectroscopy techniques, which help in

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studying the vibration transitions molecules. Raman and NIR spectra contain qualitative and quantitative information on chemical composition and physical properties of the sample. The monitoring of pharmaceutical process through NIR and Raman spectroscopy results in a huge amount of spectral data. The chemo metric technique explains the variations in the data obtained through NIR and Raman spectroscopy. These two process analyzers have the ability to supply versatile and multivariate information. The following delves the various methods of NIR and Raman spectroscopy and its effectiveness.

AN OVERVIEW OF PAT TOOLS PROCESS ANALYTICAL TECHNOLOGY

PAT is defined by the US FDA[1] as a "method for designing, evaluating, managing and producing through timely measurements of good quality and performance characteristics of raw materials and procedures with the objective of end product quality". The objective of PAT is to be aware of the manufacturing process, which includes chemical, physical, microbiological, and mathematical and risk analysis performed in a combined method.

The current approach of US FDA[1] on drug quality is that quality cannot be examined into products rather it should be built-in or should be by designed. The final products are tested on the basis of statistical sampling and testing in order to confirm the specified standard. The quality of drug testing often requires a destructive test. The complications are higher in the end product testing as the testing is only possible after the completion of batch[3]. The tools for PAT are characterized as multivariate tools for design, data acquisition and analysis, process analyzers, process control tools and constant improvement and knowledge management tools. The combination of the few tools or all these tools may be applicable to a single or entire manufacturing process[1].

PROCESS ANALYZERS

Some articles[4] identify that the availability of process analyzer tools have advanced from the tools that take univariate process measurements like pH, temperature and pressure in the biological, physical and chemical attributes. The measurements are categorized as in-line, on-line and at-line; in the at-line measurements the sample is completely removed, separated and examined in close proximity to the process stream, in on-line measurements the sample is diverted from the process and returned to the process stream, in the in-line measurements the sample is not removed from the process stream and can be persistent or non-persistent.

The process analyzers are more advanced, making high time control on the quality assurance during the manufacturing process. The process analyzers tools must be used in a grouping with multivariate methods to eradicate the complex process knowledge for high time control and quality assurance. The underlying steps or transformations related with the help of a sensor based "process signature". The process signatures help for process monitoring, control and end-point determination based on the level of understanding the process. The process tools, process analyzer and interface must be strong, dependable and have no difficulty of operation[1].

NEAR INFRARED SPECTROSCOPY (NIR)

The possibility of evolution to higher excited states ($>v_1$) is considerably lower compared to evolution to the first excited vibration energy state (v_1), which is one of the advantages of NIR spectroscopy. The NIR spectroscopy can record the spectra without any preparation of sample while in the mid-infrared spectroscopy the sample is diluted for analysis due to the high level of absorption. The molar observation in the NIR spectroscopy is 10-100 times weaker than the mid-infrared spectroscopy and it is another disadvantage of NIR spectroscopy. The radiation in the NIR region has higher penetration depth than the mid-infrared radiation[5].

The infrared spectrum envelops the wavelength range from around 700 nm to 1000 µm. The term infrared is referred as a wide range of wavelengths, beginning at the top end and extending to the lower wavelength used for communication at the end of the visible spectrum[6]. The infrared spectrum is classified into three parts such as far infrared (50-100 µm) which are longer wavelengths, mid-infrared (3-50 µm) and near infrared (700-3000 nm) which is contiguous to the visible spectrum.

The vibration spectroscopy relies on the notion that atom-to-atom bonds within molecules vibrate with frequencies and it is illustrated by the physics law and is subject to calculation[7]. The NIR spectroscopy is useful for qualitative and

quantitative analysis of water, alcohol, amines and any compounds containing C-H, N-H and O-H groups[6]. The statistical methods are used in NIR spectroscopy for interpretation in order to obtain qualitative and quantitative information from the spectra because the NIR spectra frequently contains broad bands and thus result in the individual overlapped peaks. The NIR spectroscopy has been proved as a powerful tool for research in agriculture, food, pharmaceutical, chemical, polymer and petroleum industries[8].

Table:1 Showing the Electromagnetic Spectrum(Adapted[6])

The Electromagnetic Spectrum	
Designation	**Wavelength Range**
Gamma Ray	<0.05 Angstroms
X-ray	0.05-100 Angstroms
Far-Ultraviolet	10-180 nm
Near-Ultraviolet	180-350 nm
Visible	350-700 nm
Near Infrared	700-3000 nm
Middle Infrared	3-50 µm
Far Infrared	50-1000 µm
Microwave	1-300 nm
Radio Wave	>300 nm

RAMAN SPECTROSCOPY

The energy absorption by a molecule may leads to enter a highly virtual energy state due to the monochromatic light from laser source. Later, the molecule can relax back to the ground elastic state by producing same amount of energy that was taken up previously and resulted in elastic scattering. The small parts returning to a different energy level than the incident one is called as inelastic scattering. The inelastic scattering can direct to a higher energy (strokes shift) or lower energy (anti-strokes shift) state of molecule based on the incident energy state of the molecule. The strokes shifts are reported in the Raman spectroscopy because of the greater intensity. The Raman spectroscopy is applicable as in-line and helps to obtain the real time data; it is frequently used in pharmaceutical unit operations on a molecular level[9]. The Raman spectroscopy has expanded its application in characterizing PITs of an API in final tablets and quantifying API content in tablets[10].The coating variability and thickness are also investigated through Raman spectroscopy and it is found to be an effective method for identifying fake pharmaceutical products[11].

IMPLEMENTING PAT IN THE PHARMACEUTICAL INDUSTRY

The pharmaceutical production involves the manufacture of the finished product, pursued by laboratory analysis for the quality verification. The disadvantages of continuous process optimization; persisting manufacturing difficulties and the possibility of failed batches has invited a new mode of operation to address these concerns. The mode of operation was invited by Food and Drug Administration (FDA) known as Process Analytical Technology (PAT). The PAT involves various methods and analysis in the pharmaceutical industry. The essentials of PAT and the implementation of process analyzers and its effectiveness in process monitoring are discussed. Similarly, the effectiveness of NIR spectroscopy than the Raman spectroscopy is analyzed.

PROCESS ANALYTICAL TECHNOLOGY

As per the guidance of FDA, risk analysis is one of the essentials of PAT being adopted by the pharmaceutical industry. The PAT identifies the quality of the pharmaceutical product rather than testing the quality of the finished batch. In PAT, the variables of the critical product quality are identified from the historical data. PAT engages the use of raw material properties, manufacturing parameters, and process monitoring and chemo metric techniques for producing the finished products of adequate quality. The vital point of PAT is to produce the product quality information in high-time. PAT helps in understanding and

controlling the manufacturing process and the built-in system of PAT identifies the defects in the process manufacturing rather than testing on the finished products[12].

The following sequential aspects are essential for the successful implementation of process analyzer into process streams.

- The selection of appropriate process analyzer or grouping of balancing process analyzer for monitoring the desired critical process and information of product.
- The determination of process analyzer location in the process stream like where and how the process analyzer can be implemented to monitor the information required.
- Determination of process analyzer's optimal measurement conditions in order to obtain the data.
- Validating the performance of the process analyzer streams.

The implementation of process analyzer in the chemical manufacturing plant involves huge investment, time, effort and money. The implementation of analyzer is very complex both technically and organizationally, which requires co-ordination of resources and people across various organizational, functional and geographic boundaries. The successful implementation of process analyzer helps to save the huge amount of investment and to improve the quality, which is unattainable previously. The wrong implementation of analyzer leads to a loss for an organization and lasts bad opinion among the people invested in the project and may get black mark on their records. It is essential to maintain the most important factors that determine the project successful rather than focusing on failure and it is important for the process analytical operator to ensure the successful implementation. The factors that increase the chance of failure of analyzer implementation is identified and monitored. The process analyzer implementation is broadly applied to all the technologies in general and can also be applied to the existing analyzer hardware. The implementation of process analyzer involves huge challenges, which are difficult to anticipate, and it is essential for the process analyst chemist to recognize and address the challenges as early as possible.

Table: 2 Showing the Commonly applied PAT techniques to Pharma Unit Operations

Unit Operation or Process Step	In-Line, At-Line, Off-Line Technique
Raw Materials, Dispensing	NIR, Raman, Particle Size
Reaction Monitoring	Mid-IR, NIR, UV-Visible
Crystallization	Mid-IR, NIR, Raman, FBRM, PVM
API Drying	NIR
Nanomilling	NIR
Wet Granulation	NIR, FBRM, PVM, Acoustics, Particle Imaging
Compounding Tank	NIR, Raman, FBRM
Fluid Bed Drying	NIR
Blending	NIR, NIR Imaging, Raman
Lubrication	NIR, LIBS
Compression	NIR, Raman, NIR Imaging, LIBS, Tera-hertz, LIF
Coating	NIR, LIBS, Tera-hertz
Roller Compaction	NIR, Pressure Sensors, Particle Size
Hot Melt Extrusion	NIR, Raman, UV/Vis, Fluorescence
Spray Drying	FBRM
Packaging	Reflectometry
Adjuvants	Turbidity
Fermentation	Mid-IR, NIR, Sensors
Freeze Drying/ Lyophilization	NIR, Raman
Chemometrics Software	SIMCA, Unscrambler, MATLAB
Integrated Data Network	Siemens SIPAT, SynTQ, ABB xPAT, Symbion
Reference Methods	HPLC, GC, Karl Fischer, LOD, Particle Size

PROCESS ANALYZER

The process analyzers are essential tools of PAT used for real-time process monitoring and control. They supply data through which significant process and information of product and conclusions are extracted. The tools predominantly obtain the univariate process measurements like pH, temperature and pressure to the multivariate information related to biological, physical and chemical features of the processed materials (Ex. NIR and Raman spectroscopy). The process analyzers have been mostly used for real-time measurements of complex process and attributes of product during the pharmaceutical processing. The NIR and Raman spectroscopic techniques permit quick and non-destructive measurements without preparations of sample. The implementation of spectrometers with fibre optic cables helps into the process streams permits continuous real-time in-process measurements. The ability of the process analyzer is to deliver versatile and multivariate information. The process analyzers have been used in-line, at-line and on-line to monitor and control the pharmaceutical production processes in high-time[13].

The process analyzer is an essential tool within the PAT framework and used for the purpose of monitoring the Critical Process Parameters (CPPs). The CPPs are identified through risk analysis and close monitoring and control is required for achieving the desired quality. Based on the criticality of the process step, it is necessary to keep the process parameters within distinct specifications. The in-line and on-line process analyzer provides real-time data for exceptional control process and it results in the high quality production.

NEAR-INFRARED SPECTROSCOPY (NIR)

The NIR spectroscopy has achieved broad acceptance in different fields due to its advantages over other analytical techniques. The most salient features of NIR spectroscopy is that the ability to document spectra for solid and liquid samples with no prior manipulation. The improvements in instrumentation have paved the way for manufacture of spectrometers able to quickly provide spectra that are flexible to use in different situations. It provides spectra quickly and forecast physical and chemical parameters from a single spectrum. This instrumentation has changed severely in reaction to the necessity for speed in analysis and flexibility to adapt to different sample states. Spectrometers used to document NIR spectra are crucially identical with those employed in other regions of electromagnetic spectrum. The equipment of NIR can incorporate a variety of devices based on the feature of sample and the particular analytical conditions and needs such as speed, sample and environmental conditions. The NIR spectroscopy is flexible compared to other techniques.

RAMAN SPECTROSCOPY

Raman Effect is too weak and so there is a major problem in separating the Raman's effect from the intense Rayleigh scattering. So there is a need of using multiple filters to filter the stray light. Obtaining a single Raman spectrum takes a considerable amount of time. This slows down the planned manufacture activity which uses Raman spectroscopy. Raman Effect can be viewed only on solid, liquid and gas and not on metals and alloys, so the effect cannot be used in the manufacturing process which involves metals and alloys. Identification of Raman's effect requires heating of the material by intense laser radiation; this may actually cause damage to the material itself. So Raman spectroscopy cannot be used on such raw materials. A colored material absorb the laser beam and emits fluorescence, this strong fluorescence spoils the Raman spectrum. There is difference in Raman signal when it is used in single molecule and same molecule in bulk volume. Raman signal in single molecule is five to six times larger than the same molecule in bulk level, this makes the Raman spectrum difficult to use for practical purposes.

NEAR INFRARED SPECTROSCOPY VS RAMAN SPECTROMETER

The NIR spectroscopy has been increasingly adopted in various fields as an analytical tool and has outdated the traditional technology. The NIR spectroscopy is effective and reliable than Raman spectrometry because it is a non-invasive and non-destructive technique. It requires very minimal or sometimes no sample preparation and with the help of appropriate device the solid samples can be directly measured with the help of little pre-treatment or no pre-treatment. The measurements and delivery of the result are very fast and the remarkable developments in NIR equipments and

chemo metrics used in conjunction with computers have facilitated the real-time extortion of information from the samples. The automation of technique reduces the costs and amortization time and there is no need of materials to prepare the sample. The single spectrum in NIR spectroscopy permits various analytics to be determined simultaneously. The instruments of NIR are most appropriate for the process controls at production plants. The spectrometers with fibre optics present vigorous and strong sensors for in-line, at-line and on-line control process. The NIR spectroscopic results are accurate compared to the other analytical techniques and their accuracy is also higher and sample treatment is not necessary in the NIR spectroscopy. The analytical techniques is applied in various sectors like pharmaceutical, clinical, petrochemical, agricultural food sector and other miscellaneous sectors and it is found to be successful in all these sectors.

Raman spectroscopy is highly weak during the absence of resonance and surface development and it is highly possible for fluorescence. The possibility of the Raman effects is just about 10^{-6} – 10^{-9} per incident photon, which enforces the necessity for sensitive and optimized light detectors. It is possible to eliminate the fluorescence from the previously recorded Raman spectra using numerical methods or space resolved Raman spectroscopy. Typically, obtaining Raman spectra entails shifting the sample in a step-by-step process until the whole region of interest is characterized.

CONCLUSION

PAT is a rebellion in the pharmaceutical industry initiated by the United States Food and Drug Administration to decrease the risk of producing a deprived quality product and unwanted deviations associated. As PAT is the built-in technology which tests the quality of the drug on the manufacturing process rather than testing the finished product, making high time control on the quality assurance during the manufacturing process. NIR and Raman spectroscopy are two of the effective tools of PAT which is useful in the process monitoring for the manufacturing process. Though According to the research methodology NIR spectroscopy is found more effective and reliable than the Raman spectroscopy as NIR spectroscopy has been increasingly adopted in various fields as an analytical tool and it is also found more important in the manufacturing process. The NIR spectroscopic results are accurate compared to other analytical technique (Raman spectrometer) used in the manufacturing process. And from the research it is clear that NIR is found more competent process analyzer, which can be implemented in most of the manufacturing process compared to Raman. Similarly, its successful implementation of process analyzer is very essential and the most important factors that determine the project successful rather than focusing on failure and it is important for the process analytical operator to ensure the successful implementation.

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