

Review Article

Process Analytical Technique (PAT): An Integral Part of Pharmaceutical Process Automation

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Abstract

Process Analytical Technology (PAT) is a system for designing, analyzing and controlling manufacturing process through timely measurements of critical quality and performance attributes of raw materials, in-process materials and processes with the goal of ensuring final product quality as well as reducing manufacturing costs, thereby significantly benefiting the Pharmaceutical Industry in manufacturing area. PAT involves the use of different technologies and tools to build quality into the products. Different techniques are described for typical steps in the production of drug substance and drug product. These methods are mainly based on spectroscopy and other optical sensors, in combination with chemometric multivariate data

evaluation tools. Pharmaceutical companies face many challenges while implementing PAT into their new and pre-existing manufacturing processes. To make the Pharmaceutical process Automation effective the implementation of Process Analytical Technique (PAT) in the Process is very important to avoid human interference. So this review includes discussion about the PAT in details which is very important.

Keywords: Process Analytical Technique, Chemometric, Quality by Design, US FDA.

INTRODUCTION

When we talk about Automation in consumer segments, automobile industry has already taken a huge leap in past and the controls today has almost reached to a level of six-sigma. The second and Similar level of automation and control can be seen in food industry these days where advanced technologies and control level has brought the quality level of final product into the band of well controlled limits. On the other side when we look over the need vs. actual controls in pharmaceutical industry there is currently a huge gap^{1,2}. When we talk about level of quality in pharmaceutical we can assume it to be more or less equivalent to quality standards in automobile because the efficacy of medicines is directly linked to the survival and health of patients. For example, a one month dose of medicine with reduced drug content can lead to increased symptom of ongoing medical condition and hence severe health disorder. Now, it's high time for pharmaceutical industry also to take a leap of faith towards building full automation and control into processes so as to provide the end consumer with more effective and consistent quality of efficacy with the required drug product. It's time for the industry to start coming at par with the automobile industry. In this chapter we will take this concept forward and discuss in more detail about the challenges and solutions in bringing full automation and control in Pharmaceutical industry^{3,4}.

Challenges and solutions in achieving complete automation in pharmaceutical processes:

The various challenges are needed in achieving complete automation in Pharmaceutical processes are regulatory challenges, process complications, lack of skill set in process control & automation,

cost versus quality and lack of sufficient development and scale-up tools. One of the most appropriate and scientific solution is the implementation of Process Analytical Technique in the pharmaceutical process. Let us talk one by one about the challenges involved in moving steps forward towards complete automation in pharmaceutical^{5,6}.

Regulatory challenges:

As the competition grows in pharmaceutical industry, especially in generics business, lot of non-compliance issues are growing and being observed by regulatory agencies across globe. Quality is being compromised in the race to launch products on time and make quick deliveries. In view of these growing observations regulatory agencies have started to become more stringent and pressurizing the industry to manufacture products with more process controls and more compliance. The expectations are growing day by day and regulatory have started to take strict actions against cases where even minor non-compliances and process control gaps are observed. The manual procedures involved in certain unit operations are being challenged by regulatory and such processes are at stake towards successful validation in near future. Even applying a proper solution by converting part processes into automated one may call for a re-validation of existing products and again a risk to create an array of queries from regulatory agencies. Now it is high time to intervene and find an appropriate solution to answer such queries and build up a system that can help in putting a tight control end to end so as to avoid falling in the hands of regulatory agencies. We will discuss in more detail about the remedies and ways to put such system successfully in place along with all the challenges⁷⁻⁹.

Process complications:

When we look over the process controls in food industry and the need for quality over there, there is not a mismatch and the processes are well under control taking care of all the complications and challenges. But, when we see the pharmaceutical processes as such, there is still lot of mismatch between process control and the need for quality. Also, needless to say the required level of quality standard is much more as compared to food industry. There are many factors that make the pharma-

ceutical processes more complicated. One of them is the fact that the impact of all critical process parameters on the finished dosage quality such as drug release rate and assay is so large that even small variations in few parameters result in huge variation in final quality¹⁰.

API manufacturing processes do have adopted few controls such as DCS (distribution control system) based system but still there are lot of gaps involving manual interruptions in almost all operations. Even in formulation processes there are lots of process complications that result in difficulty to define an appropriate method to control final quality. Let us consider 2 examples of steps involved in 2 different unit operations in formulations^{11,12}.

- (a) Binder addition step in high shear granulation – It is very critical in few products to keep the binder addition rate in high shear granulation process to a controlled limit but unfortunately it is difficult to do so at commercial scale because the rate is very high and there are always pump and tube limitations to control this accurately.
- (b) Defining blending time – In critical products involving segregation tendency it is very difficult to define exact blending time and blender speed as even factors such as sequence of material addition in the bin can affect exact mixing time.

For Pharmaceutical dosage form earlier days concept of Quality determination was by testing only, means from a batch of dosage form few Random quantity of batch representative samples will be withdrawn for testing, results will determine the quality of the product. But the quality of each unit dosage is very important in respect to the end user's desired purpose, So Now the recent concept of Quality is 'Quality by design', (QbD) So that the quality is inbuilt by design. It means the design of Specifications of raw material, packing material, Finished Goods and the Formulation design, Process design, Process Parameters space design etc are to be considered or designed scientifically by using the relevant and effective scientific tools to maintain quality by design throughout the product life cycle. So to fulfill the QbD requirement the PAT Tool is also very important & integral part of QbD in the area of Process Control and Automation¹³⁻¹⁵.

Process Analytical Technique (PAT):

PAT is an Advance tool for designing, analyzing and controlling Pharmaceutical Manufacturing Process through timely measurements (i.e. on line, off line, in line) of Critical Quality and performance attributes for raw and in process materials and processes with the objective of ensuring the product desired quality. PAT shows its importance as it effectively builds quality into products; also eliminate the process variation resultant into process safety. It also helps to understand the manufacturing process and its control in totality¹⁶.

Different levels of PAT Implementation:

The different stages of PAT implementation includes capturing of manufacturing process parameters (Preliminary stage), evaluation of process parameters data (Scale up stage), process understanding (Provisional stage) and actual process monitoring and process control by implementing PAT tools (Permanent stage).

PAT analysis is preferred over conventional laboratory analysis due followings reasons are faster or online results are available , which helps to take the decision to release the batches for the consumption, PAT eliminate the human error, it is safe to product , human and environment, it increases the productivity and during analysis sample integrity exists¹⁷.

PAT Tools – Off line:

PAT tools are used for various purposes like powder flow meter, to characterize the powder physical properties like flow rate and angle of repose. Similarly powder rheometer is used to characterize the Powder physical Properties and measures the energy and force like basic flow energy, aeration energy, permeability energy, compressibility, shear cell force, wall friction force and stability energy.

PAT tools exhibit several benefits like it improves the productivity; it exterminates the human intervention as a result upturns the automation, it ensures the operator's safety, it corrects on line the process variation so resultant into elimination of the variability in the process and it creates the data bank and in turn guides for continuous improvement plan.

PAT tools possess various limitations like it needs specialized and expertise hand to implement, it needs a long term implementation plan, it requires skill, patience, passion & dedication of the process analyst, it needs efforts during design and implementation and initial capital investment is costly^{18,19}.

How to make PAT effective in the Industry²⁰:

PAT can be made effective in industry by adopting various approaches like selection of process, selection of suitable PAT tools, identification of critical process parameters and design process followed by on-line test, off-line test and in-line test.

Table-1: PAT applications in pharmaceutical process.

Unit Operation	PAT Tools (On Line)
Raw Material Identification	Near Infra Red (NIR), Raman
High Shear Wet Granulation process	Torque meter, NIR, PARSUM, Acoustic Emission , FBRM
Low shear Wet Granulation (FBP)	PARSUM, FBRM, NIR
Reaction Monitoring	NIR
Crystallization	FBRM
Fluidized Bed Drying	NIR
Mixing, Blending and Lubrication	NIR
Tablet Compression	NIR
Coating	Droplet Size measurement, NIR

Quality of process analyst as PAT Implementer²¹:

- Should be passionate and having strong determination about PAT.
- Should have high level Knowledge about PAT.

- Should have learning, initiative, interpersonal skill, Data analysis skill.
- Should be innovative, focus to the objective.
- Overall should be good leader.

Regulatory agency's guidance and acceptance²²:

- US FDA published the PAT Guidance in September 2004 for industry.
- All Regulatory agents appreciate the PAT approach.
- PAT can be used as a quality measurement tool as replacement to conventional method.
- To implement PAT tool as an alternate Quality detection device in the pharmaceutical process an applicant has to apply to regulatory agency through an application form will trigger the inspection by competent team followed by the approval for the PAT tool usage as an alternative Quality Detection Device.

CONCLUSION:

Process analytical technology (PAT) is used to monitor online and control critical process parameters in raw materials and during the manufacturing of active pharmaceutical ingredients and drug products. The PAT initiative encourages the pharmaceutical industry to embrace new analytical approaches with the aim of transforming process development automated control are essential elements of this change which has the potential to improve product quality, reduce production costs and time to market. A knowledge base created through the collection, analysis and evaluation of research, development and manufacturing data facilitates the justification for a science and risk based approach to analytical method validation and process monitoring and control.

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