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Chemometrics in process analytical technology

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ABSTRACT

The requirement for enhancing healthcare products is eternally increasing. In this regard, the requisite for monitoring all the physical and chemical attributes during the manufacturing of the health care products with a lesser time is truly essential. A new tool, Process analytical technology (PAT) is used to monitor and control critical process parameters in materials and in-process products to maintain the critical quality attributes and build quality into the product. Process Analytical Technology checks the quality of the materials on-line, which saves a huge amount of time and facilitates rapid testing through direct sampling without any destruction of sample. However, to successfully adapt PAT tools into pharmaceutical and biopharmaceutical environment, thorough understanding of the process is needed along with mathematical and statistical tools to analyze large multidimensional spectral data generated by PAT tools. Chemometrics is a chemical discipline which incorporates both statistical and mathematical methods to obtain and analyze relevant information from PAT spectral tools. In this article, Process Analytical Technology is briefly introduced and commonly used PAT tools in combination with appropriate chemometric methods along with their advantages and working principle are discussed.

Key words: Process Analytical Technology (PAT), Chemometrics, Pharmaceutical, Tools.

INTRODUCTION

Process Analytical Technology (PAT) is a mechanism to design, analyze and control manufacturing processes through timely measurements of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring product quality. PAT allows for and encourages continuous process manufacturing improvement. It includes chemical, physical and microbiological mathematical and risk analysis conducted in an integrated manner.

It uses real time information to reduce process variation and manufacturing capability and demands a solid understanding of the various processes involved in the operation.

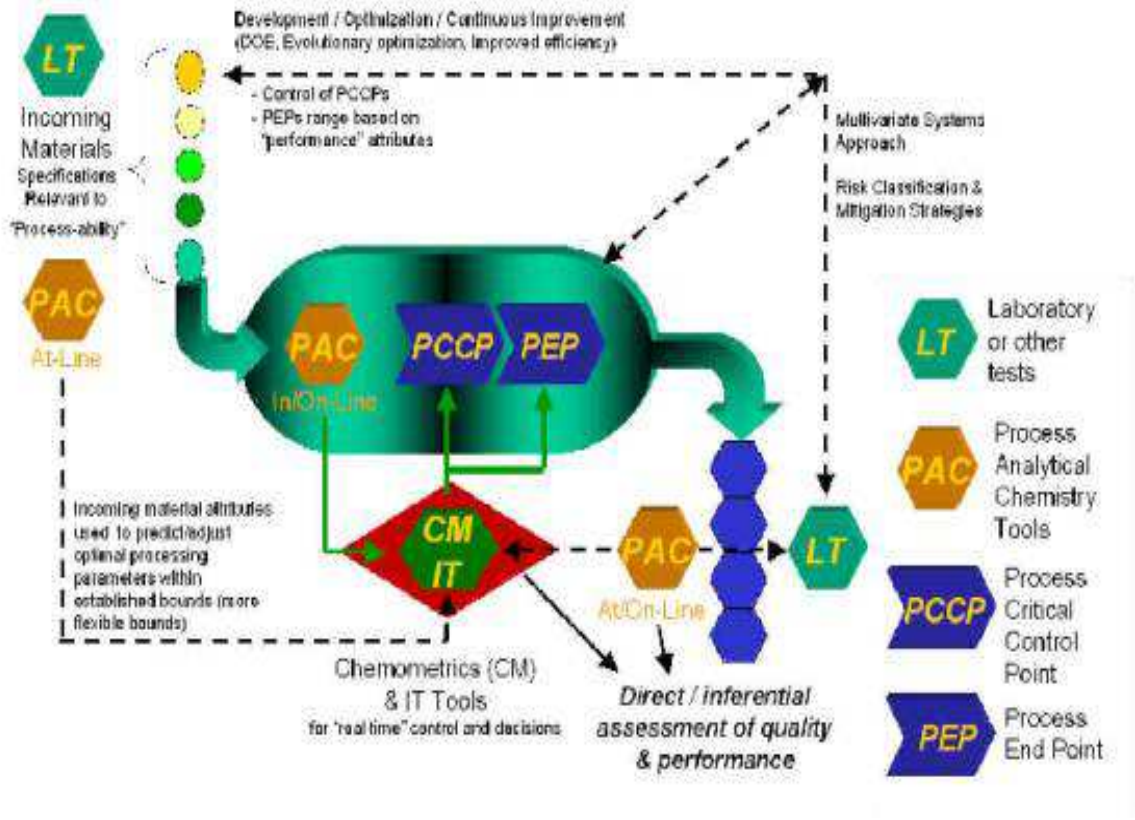
The concept aims at understanding the processes by defining their CPPs, and accordingly monitoring them in a timely manner (preferably in-line or on-line) and thus being more efficient in testing while at the same time reducing over-processing, enhancing consistency and minimizing rejects.

The primary goal of PAT is to provide processes which consistently generate products of a predetermined quality. Effective PAT implementation is founded on detailed, science-based understanding of the chemical and mechanical properties of all the elements of the product. In order to design a process that provides a consistent product, the chemical, physical and biopharmaceutical characteristics of the drug and other components of the drug product must be determined. The role of on-line advanced measurement systems is pivotal to realizing the benefits of PAT. However, the transformation of process performance to provide greater efficiency and cost effectiveness, in addition to assured quality, requires much more than the application of measurement technologies.

Processing to a quality based end point is a key part of PAT quality assurance regime. This eliminates wasted cycle time associated with processing using a fixed time based end point including subsequent reprocessing time and provides a stream lined work flow through the facility.

Process Analytical Technology or PAT, is intended to support innovation and efficiency in pharmaceutical development, manufacturing, and quality assurance. The frame work is founded on process understanding to facilitate innovation and risk-based regulatory decisions by industry and the Agency.

The framework has two components: (1) a set of scientific principles and tools supporting innovation and (2) a strategy for regulatory implementation that will accommodate innovation.



(Fig-1)

However, today significant opportunities exist for improving pharmaceutical development, manufacturing, and quality assurance through innovation in product and process development, process analysis and process control.

Therefore, pharmaceutical manufacturing will need to employ innovation, cutting edge scientific and engineering knowledge, along with the best principles of quality management to respond to the challenges of new discoveries (e.g., novel drugs and nanotechnology) and ways of doing business (e.g., individualized therapy, genetically tailored treatment).

Regulatory policies must also rise to the challenge. It is important to note that the term *analytical* in PAT is viewed broadly to include chemical, physical, microbiological, mathematical, and risk analysis conducted in an integrated manner.

Process Analytical Technology tools:

There are many current and new tools available that enable scientific, risk-managed pharmaceutical development, manufacture, and quality assurance. These tools, when used within a system can provide effective and efficient means for acquiring information to facilitate process understanding, develop risk-mitigation strategies, achieve continuous improvement, and share information and knowledge.

In the PAT framework, these tools can be categorized as:

- Multivariate data acquisition and analysis tools.

- Modern process analyzers or process analytical chemistry tools.
- Process and endpoint monitoring and control tools.
- Continuous improvement and knowledge management tools.

An appropriate combination of some, or all, of these tools may be applicable to a single-unit operation, or to an entire manufacturing process and its quality assurance.

A desired goal of the PAT framework is to design and develop processes that can consistently ensure a predefined quality at the end of the manufacturing process. Such procedures would be consistent with the basic tenet of quality by design and could reduce risks to quality and regulatory concerns while improving efficiency.

Gains in quality, safety and/or efficiency will vary depending on the product and are likely to come from:
- Reducing production cycle times by using on-, in-, and/or at-line measurements and controls.
- Preventing rejects, scrap, and re-processing.
- Considering the possibility of real time release.
- Increasing automation to improve operator safety and reduce human error.
- Facilitating continuous processing to improve efficiency and manage variability.
- Using small-scale equipment (to eliminate certain scale-up issues) and dedicated manufacturing facilities.
- Improving energy and material use and increasing capacity.

Background:
Chemometrics may be regarded as the application of statistical and mathematical methods to research challenges in chemistry using modern information and communication technology. A typical application of chemometrics is the multivariate data analysis of the analytical data obtained in research project in the process analytical chemistry or environmental chemistry.

These methods are, for example, Principal Component Analysis (PCA) and Partial Least Squares Regression (PLS regression). The application of modern PAT technology (PAT, process analytical technology) to pharmaceutical manufacturing processes demands the use and knowledge of appropriate chemometric tools.

The goal of Process Analytical Technology is "to understand and control the manufacturing process, which is consistent with our current drug quality system. Chemometrics and its methods are versatile and there is a high level of abstraction as it characterizes the scientific disciplines extensively by the application of the statistical and mathematical methods, mainly the multivariate methods.

The statistical tools which are commonly implemented in PAT are provided below.
1. **Partial Least Squares (PLS)**
2. **Principal Components Analysis (PCA)**
3. **Multivariate analysis.**

Partial least square (PLS):
Partial least square is the most popular chemometric tool used in process analytical technology. PLS is the method for constructing predictive models when the factors are many and highly collinear. For example, PLS is not usually appropriate for screening out factors that have a negligible effect on the response. However, when prediction is the goal and there is no practical need to limit the number of measured factors, PLS can be a useful tool. PLS has been applied to monitoring and controlling industrial processes; a large process can easily have hundreds of controllable variables and dozens of out-puts.

The advantages of PLS regression is:
a) Deals with multicolinearity.
b) Allows taking into account the data structure.
c) Provides visual results that help the interpretation.
d) Can model several response variables at the same time taking into account their structure.

Principle component analysis (PCA):
PCA is a simple, nonparametric method for extracting relevant information from datasets, identifying patterns in data, and expressing the data in such a way to highlight their similarities and differences. PCA is applied for the reduction of dimensionality and multivariate data compression exploration within different fields of science. It is one of the widely used multivariate methods because of its wide applicability in the multivariate problems.

Importance of PCA is manifested by its use in so many different fields of science and life. During the monitoring of a process, PCA can be used to find a correlation structure of variables and to examine the changes in variable correlations and hence is used for reducing the number of variables in a process. In PCA, data is transformed to describe the same amount of variability.

The advantages of PCA are:
A primary benefit of PCA arises from quantifying the importance of each dimension for describing the variability of a data set. PCA can also be used to compress the data, by reducing the number of dimensions, without much loss of information.

When using principal component analysis to analyze a data set, it is usually possible to explain a large percentage of the total variance with only a few components. Principal components are selected so that each successive one explains a maximum of the remaining variance, the first component is selected to explain the maximum proportion of the total variance, the second to explain the maximum of the remaining variance, etc. Therefore, the principal component solution is a particularly appropriate test for the existence of a strong market factor.

PCA is completely nonparametric: any data set can be plugged in and an answer comes out, requiring no parameters to tweak and no regard for how the data was recorded. From one perspective, the fact that PCA is non-parametric (or plug-and-play) can be considered a positive feature because the answer is unique and independent of the user.
PCA is a special case of Factor Analysis that is highly useful in the analysis of many time series and the search for patterns of movement common to several series. This approach is superior to many of the bivariate statistical techniques used earlier, in that it explores the interrelationships among a set of variables caused by common "factors," mostly economic in nature. PCA is a way of identifying patterns in data, and expressing the data in such a way as to highlight their similarities and differences.

Multivariate analysis (MVA):
Multivariate analysis (MVA) is based on the statistical principle of multivariate statistics, which involves observation and analysis of more than one statistical outcome variable at a time.

Multivariate techniques are used to study datasets in consumer and market research, quality control and quality assurance, process optimization and process control and research and development. Multivariate techniques can statistically estimate relationships between different variables and correlate how important each one is to the final outcome and where dependencies exist between them.

There are several different multivariate techniques to choose from based on assumptions about the nature of the data and the type of association under analysis. Each technique tests the theoretical models of a research question about associations against the observed data. The theoretical models are based on facts plus new hypotheses about plausible associations between variables.

Uses for multivariate analysis include:
- Design for capability (also known as capability-based design).
- Inverse design, where any variable can be treated as an independent variable.
- Analysis of Alternatives (AoA), the selection of concepts to fulfill a customer need.
- Analysis of concepts with respect to changing scenarios.
- Identification of critical design drivers and correlations across hierarchical levels.

Multivariate techniques allow researchers to look at relationships between variables in an overarching way and to quantify the relationship between variables. They can control association between variables by using cross tabulation, partial correlation and multiple regressions and introduce other variables to determine the links between the independent and dependent variables or to specify the conditions under which the association takes place.

This gives a much richer and realistic picture than looking at a single variable and provides a powerful test of significance compared to univariate techniques.

The disadvantages of Multivariate techniques are;
Multivariate techniques are complex and involve high level mathematics that requires a statistical program to analyze the data. These statistical programs are generally expensive. The results of multivariate analysis are not always easy to interpret and tend to be based on assumptions that may be difficult to assess.

For, multivariate techniques to give meaningful results they need a large sample of data; otherwise, the results are meaningless due to high standard errors. Standard errors determine how confident you can be in the results, and you can be more confident in the results from a large sample than a small one. Running statistical programs is fairly straightforward but does require a statistician to make sense of the output.

CONCLUSION

Various chemometric models have been applied for the analysis of data of a particular manufacturing process, quality control test, or an instrumental output data with an aim to achieve maximum accuracy, precision, and robustness. The chemometric methods are expected to provide a rapid quantitative analysis of pharmaceutical properties of intermediate and finished dosage forms as characterized by the simple, nondestructive, and highly sensitive nature of the method. Pharmaceutical industrial viability of chemometric techniques could range from setting quality control specifications for raw material, powders, and dosage forms to control of various manufacturing processes and steps. The implementation of chemometric techniques with a view of ensuring overall production process control entails the use of analytical techniques capable of providing accurate results in a simple and rapid manner.

REFERENCES

[1] S. Matero, Chemometrics Methods in Pharmaceutical Tablet Development and Manufacturing Unit Operations, Publications of the University of Eastern Finland Dissertations in Health Sciences, **2010**.
[2] I. T. Jolliffe, *Principal Component Analysis*, Springer, New York, NY, USA, 2nd edition, **2002**.
[3] A. Hoskuldsson, *Journal of Chemometrics*, vol. 2, pp. 211–228, **1988**.
[4] R. Manne, *Chemometrics and Intelligent Laboratory Systems*, vol. 2, no. 1–3, pp. 187–197, **1987**.
[5] J. Nilsson, S. De Jong, and A. K. Smilde, *Journal of Chemometrics*, vol. 11, no. 6, pp. 511–524, **1997**.
[6] R. Bro, *Journal of Chemometrics*, vol. 10, no. 1, pp. 47–61, **1996**.
[7] A. Hoskuldsson, *Journal of Chemometrics*, vol. 2, pp. 211–228, **1988**.
[8] M. Barker and W. Rayens, *Journal of Chemometrics*, vol. 17, no. 3, pp. 166–173, **2003**.
[9] P. H. Garthwaite, *Journal of the American Statistical Association*, vol. 89, pp. 122–127, **1994**.
[10] Jolliffe, I. T. (**2002**). *Principal component analysis* (Second ed.): Springer.
[11] U.S Food and Drug Administration, Guidance for Industry, PAT- a framework for Innovative pharmaceutical development, manufacturing and quality assurance, September **2004**.
[12] Chew W, Sharratt P. *Analytic.Meth*.**2010**; 2:1412-1438
[13] Callis JB, illman DL, Kowalski BR*Anal.Chem*, **1987**; 59; 624A-637A.
[14] Miller CE. Chemometrics in process analytical chemistry. In process Analytical Technology: Spectroscopic Tools and Implementation Strategies for the chemical and Pharmaceutical Industries, Bakeev KA (ed). Wiley: Chichester, **2010**; 353-438.
[15] Rajalahti T, Kvalheim OM. *Int.J.Pharm*.**2011**; 417:280-290.