REVIEW PAPER

JMS Journal of Medical Science

Real-time quality control for chemical and biotechnological processes: a brief review

Agnieszka Kołodziejczak-Radzimska
Institute of Chemical Technology and Engineering, Faculty of Chemical Technology, Poznan University of Technology, Poland
https://orcid.org/0000-0002-5338-0436

Beata Rukowicz
Institute of Chemical Technology and Engineering, Faculty of Chemical Technology, Poznan University of Technology, Poland
https://orcid.org/0000-0002-1304-3638

Corresponding author: beata.rukowicz@put.poznan.pl

Sharon Davin
APC – Applied Process Company Ltd., Dublin, Ireland
https://orcid.org/0000-0003-0578-8741

DOI: https://doi.org/10.20883/medical.e901

Keywords: Process Analytical Technology (PAT); real-time process control; online analysis; monitoring techniques

Received: 2023-07-31
Accepted: 2023-09-13
Published: 2023-09-29

How to Cite: Kołodziejczak-Radzimska A, Rukowicz B, Davin S. Real-time quality control for chemical and biotechnological processes: a brief review. Journal of Medical Science. 2023;93(3);e901. doi:10.20883/medical.e901

ABSTRACT

Monitoring critical process parameters of chemical and biotechnological processes is an essential tool at every stage of drug manufacturing technology. The aim of Process Analytical Technology (PAT) is to provide effective tools, such as multidimensional data analysis, modern analytical methods, and monitoring tools, for the continuous improvement of process understanding and knowledge. Among the methods of wide interest are optical and spectroscopic techniques that can be used in the control of chemical and biotechnological processes. The selection of the appropriate method is crucial and depends on many factors, including the nature of the process, the number of variables, and analytical limitations. This review focuses on a brief and precise characterization of spectroscopic and optical methods that can be applied to monitoring and control of chemical and biotechnological processes.

Introduction

The chemical and pharmaceutical industry plays an important role in human life. In the traditional approach, the production process was controlled according to an approved protocol. Then, in order to check the quality of the completed process, compliance with the requirements of the final product was ensured by a pre-approved quality of the product itself [1, 2]. The identification and monitoring of critical parameters of both chemical and biotechnological processes is an essential tool at every stage of drug manufacturing technology. The Process Analytical Technology (PAT) strategy, as defined by the Food and Drug Administration (FDA), is based on real-time process quality control. As a result, risk analysis is not limited to analysis of the final product and takes into account the variability of raw materials, materials, and apparatus during the process [3].

Process analysis technology has been defined as a mechanism for designing, analyz-

ing, and controlling pharmaceutical production processes by measuring critical process parameters that affect product quality [4]. PAT checks the quality of raw materials both physically and chemically. PAT can be employed in the transition from checking the quality of raw materials to the quality of products, by testing the chemical and biotechnological process at several intermediate stages. PAT offers a significant reduction in time and cost spent on product sampling and analysis. The main goal of PAT is to provide effective tools, such as multidimensional data analysis, modern process analyzers or analytical methods, monitoring of final processes, and control tools for continuous improvement of knowledge [5].

This review focuses on a brief and precise characterization of spectroscopic and optical methods that allow the monitoring and control of the chemical process. In the next two chapters, the various optical and spectroscopic methods are described.

The optical methods used in process analytical methods

The production of active pharmaceutical ingredients (APIs) faces various problems, including batch inconsistency in terms of particle crystal size, number of crystal particles produced, and purity profile (residual impurities in crystals or incorrect polymorphic or chiral purity). This can have a significant impact on both product quality and downstream operations of the process unit, including filtration, drying, milling and formulation of the product [1, 2]. Particle size analyzers play an important role during process development and quality control of particle systems in order to develop efficient processes and achieve high final product quality. In the traditional approach, product inspection involves sampling and off-line particle size analysis. Laser diffraction, dynamic light scattering, microscopy, or sedimentation methods are used for this purpose. The application of optical PAT techniques drives efficiency in the sampling and analysis process. The ability to measure naturally occurring particles in the process improves the ability to understand, optimize, and control particle and droplet systems. Understanding precisely how process parameters impact concentration, size, shape, and structure of particles enables the scientist to make better decisions, eliminate process risks, and solve problems faster [3, 4]. Process analytical technology uses different optical methods that allow the chemical process to be carried out and avoid the above-mentioned problems. The following are two most common methods used to determine particle properties.

The first one is Focused Beam Reflectance Measurement (FBRM), a technology that measures particle counts and sizes in real time based on laser light backscattering. This technique allows to determine the properties of particles in suspension, emulsion, and crystallization and to monitor the changes that occur during this process (for example from solution stage to crystal formation) [6–9]. The size, distribution, shape, and growth behavior of particles in the granulation and crystallization processes can be evaluated using the FBRM method. Due to the FBMR technique, the particle properties of the finished product can be controlled and monitored in real time [10]. For example, Sorota et al. [11] outlined the development of two robust crystallization methods that deliver purified islatravir with a controlled particle size distribution (PSD) and impurity profile. In turn, Muhaimin et al. [12] use FBRM measurements to investigate the effects of the polymer type and compare the size distributions with those obtained using other sizing methods, such as optical microscope and laser diffraction. The FBRM device is equipped with a probe that is inserted directly into the process stream at a suitable angle so that particles can easily flow through the probe window where the measurement takes place (**Figure 1**). The laser beam is guided along the probe's lead through an optical system that focuses it to a small spot on the sapphire window. The optical system rotates at a constant speed, causing the beam to scan quickly the particles passing by the window. As the particle system is scanned by the focused beam, single particles or particle structures cause laser light to be backscattered towards the detector. Clearly occurring pulses of backscattered light are detected and counted, and the duration of each pulse is multiplied by the scan rate to calculate the length of the segment that intersects each particle. This quantity is called the chord length – the basic measure of a particle related to its size. Within seconds, thousands of particles

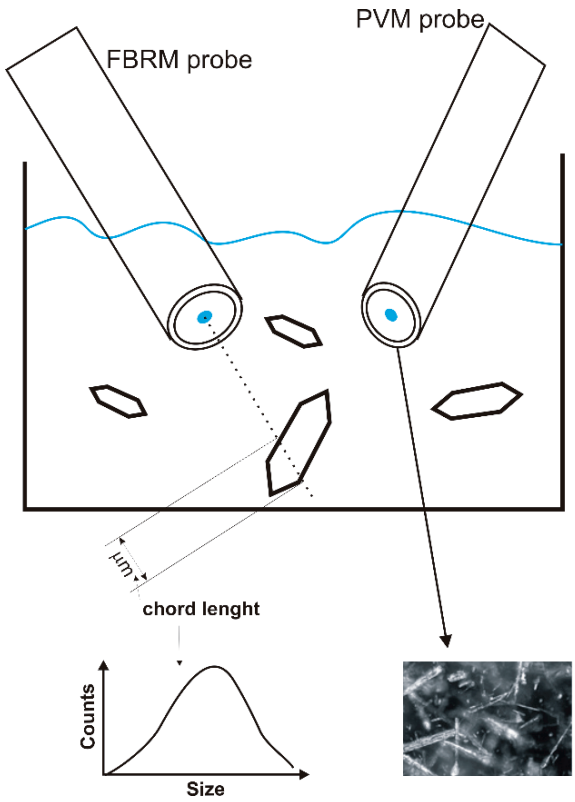

Figure 1. General schematic of the measurement using the Focused Beam Reflectance Measurement (FBRM) and Particle Video Microscope (PVM) techniques.

are counted and measured, resulting in a precise and sensitive measurement of chord length distribution, reported in real time. The chord-length distribution informs about changes in the size and number of particles from the beginning to the end of the process. Statistics on each chord-length distribution, such as the number of particles classified as fine or large, can be analyzed in terms of time trends. By varying operating conditions and tracking particles and their structures as they occur in the process, particle systems can be better understood, optimized, and controlled [13, 14].

PVM (Particle Video Microscope) is a type of online micro camera that can visually track nucleation, crystal growth, polymorphic transformation, blending, and fragmentation during a chemical process [4, 9, 15] or biotechnological process [16] in real time. In addition, color-related changes can be detected by endoscope probes. This kind of technology was used by Su et al. [17] to track the polymorphic transformation from the α to the β form of mannitol. Whereas Liu et al. [18] applied the PVM technique to study crystal growth and carbamazepine transformations.

The PVM-based instrument has a probe to visualize particles and particle mechanisms in real time. High-resolution images were obtained under different process conditions without the need for sampling or off-line manual analysis [9, 15]. The sensitivity of the process trends to changes in particle size and concentration is automatically combined with the most relevant images (**Figure 1**), ensuring that all experiments are a simple and reliable method that combines the complete understanding of the process. High-resolution in-real-time particle imaging allows one to determine the impact of process parameters on the size, number, and shape of the particles. Particles can be designed to be predictable when key parameters change during development, scaling, and manufacturing. In addition, this fast and reliable method reduces the time, total production costs, and efforts necessary to fully understand the complex particle system and process [13, 15].

In summary, it should be stated that the use of tools based on optical methods facilitates real-time process monitoring. Thanks to the FBRM and PVM methods, it is possible to track changes in the size and shape of particles during a given chemical (or biotechnological) process. This allows for control of certain processes during the crystallisation stage and introduces changes so that the production goes in the right direction.

The spectroscopic methods used in process analytical methods

Spectroscopy is a broad non-destructive analytical field that is based on the analysis of the interaction between an electromagnetic wave and an analyte via adsorption, emission, or scattering. Depending on the wavelength, spectroscopic methods can be classified as Ultraviolet-Visible (UV/Vis), Near Infrared (NIR), Mid Infrared (MIR), Far Infrared (FIR), Raman, and Nuclear Magnetic Resonance (NMR) [19]. Spectroscopic sensors integrated into upstream and downstream unit processes in *in-line*, *on-line*, or *at-line* mode enable real-time process monitoring and control. These tools are particularly important in biotechnological processes because biological drugs have a more complex structure, a less predict-

able conversion pathway, and a more dynamic nature than their small molecule counterparts [20]. Compared to optical techniques, an important aspect is also the possibility of using spectroscopic methods not only for qualitative analyzes, but also for quantitative measurements of parameters such as glucose, ammonium, lactate, and glutamate concentration, the amount of biomass or optical density [16].

NIR spectroscopy works on the principle that the atoms of molecules are in constant motion, vibrate at specific frequencies, and directly depend on the mass of each atom in the molecule and the strength of the chemical bond. Compared with IR, which detects basic vibrations, NIR measures higher-energy waves that create combined vibrations and allows the detection of weak absorbance bands where samples do not require a dilution for measurement. The advantageous high sensitivity of NIR generates spectral complexity, which is associated with the need to use multivariate statistical models to extrapolate data based on various parameters [16]. In the MIR method, the spectrum obtained can be used as a direct measurement of the components in the solution, while the disadvantage of this technique is the high interference of water, which is present in most test samples and limits accurate calibration. Raman spectroscopy provides characteristic information on molecular vibrations for analytes ranging from small molecules to biological compounds and cells. Compared to NIR or MIR, the Raman method has the advantage that water produces only a weak signal and does not overlap with peaks of interest for common analytes [21]. As a result, the Raman spectroscopic method is indicated in the literature as a potential analytical solution due to the possibility of measuring small-sized liquids, solids and gaseous samples, without prior preparation and destruction of the sample, carried out directly in reactors and bioreactors [22]. In process control, inline Raman spectroscopy in combination with multivariate statistical analysis has been identified as a potentially useful tool for advanced chemical and bioprocess development, although it has not been widely applied in industrial R&D. A solution suggested in the literature, based on the combination of Raman and IR spectroscopy as complementary methods, having different sensitivity to different functional groups, may offer an enhanced PAT approach [22, 23].

In the work of Talicska et al. [24] real-time NMR analysis was utilized to characterize the reaction components in the continuously stirred tank reactor and determine the kinetics of the Grignard reaction to monitor the bromide starting material and the Grignard reagent. The possibility of using FTIR support in the hydrogenation reaction carried out in a gas-liquid flow reactor was also demonstrated. In the case of bioprocesses, NIR and Raman methods are sensitive to the content of e.g. glucose, lactate and ammonia while cell density can be determined by MIR or UV-Vis [19].

The analysis of spectra obtained by spectroscopic methods compares control samples with test samples and the identification of regions where peak changes are observed. Spectral signals are complex and require calibration to specific process conditions. At the initial stage, it is

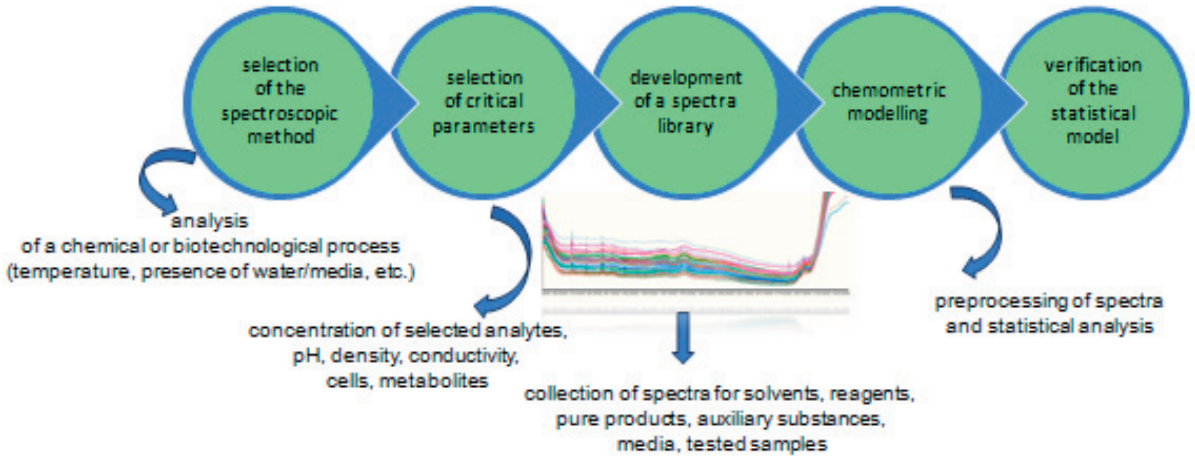

Figure 2. Scheme of PAT implementation stages using spectroscopic methods.

important to select the critical parameters (**Figure 2**). The generated spectra require preprocessing to reduce noise and other data interference. Spectral analysis can be performed using multivariate analysis methods including principal component analysis (PCA), hierarchical cluster analysis (HCA), and partial least squares (PLS). In the final stage, the developed model requires verification and calibration [25]. PAT implementation and real-time prediction of changes in critical parameters by integrating *in-line* process monitoring technology and chemometric analysis can be an important tool not only for batch processes, but also for flow systems, including reactions carried out in plug flow reactors (PFRs) and continuous stirred tank reactors (CSTRs) [24].

Conclusions

The ability to control individual operations with simple and reliable analytical tools is an important aspect in any field of technological processes. Advanced Quality by Design (QbD) tools can be used to assess risk early and predict critical product properties and process factors to improve process development and reduce costs. The emphasis on the development of control of critical process parameters is also visible in the pharmaceutical sector, where process analysis technology is an essential tool in chemical and biotechnological processes. The analysis of the literature indicates the wide possibilities of implementing optical and spectroscopic techniques as PAT tools. In addition, it is important to identify critical parameters and develop appropriate statistical models to implement accurate calibration.

Acknowledgements

Conflict of interest statement
The authors declare no conflict of interest.

Funding sources
Part of the research was funded by the European Union's Horizon 2020 Research and Innovation program under the Marie Skłodowska Curie grant agreement No 778051, and the Ministry of Science and Higher Education of Poland 5014/H2020 MSCARISE/2019/2. The views expressed in this article are those of the authors and do not necessarily reflect the European Union's or the respective institution's position on the subject.

References

1. Mali AS, Jagtap M, Karekar P, Maruska A. A brief review on process analytical technology (PAT). Int J Curr Pharm Res 2016;8:10.
2. Mazivila SJ, Santos JML. A review on multivariate curve resolution applied to spectroscopic and chromatographic data acquired during the real time monitoring of evolving multi component processes from process analytical chemistry to process analytical technology. Trends Anal Chem 2022;157:116698.
3. Nagy B, Galata DL, Farkas A, Nagy ZK. Application of artificial neural networks in the process analytical technology of pharmaceutical manufacturing—a review. AAPS J 2022;24:74.
4. Simon LL, Pataki H, Marosi G, Meemken F, Hungerbühler K et al. Assessment of recent process analytical technology (PAT) trends: a multiauthor review. Org Process Res Dev 2015;19:3.
5. Feng H, Mohan S. Application of Process Analytical Technology for pharmaceutical coating: challenges, pitfalls, and trends. AAPS Pharm Sci Tech 2020;21:179.
6. Hou G, Power G, Barrett M, Glennon B, Morris G, Zhao Y. Development and characterization of a single stage mixed suspension, mixed-product-removal crystallization process with a novel transfer unit. Cryst Growth Des 2014,14:1782.
7. Kyoda Y, Costine A, Fawell P, Bellwood J, Das G. Using focused beam reflectance measurement (FBRM) to monitor aggregate structures formed in flocculated clay suspensions. Miner Eng 2019;138:148.
8. Bodmeier R. Effect of solvent type on preparation of ethyl cellulose microparticles by solvent evaporation method with double emulsion system using focused beam reflectance measurement. Polym Int 2017;66:1448.
9. Melchuna A, Cameirao A, Herri J-M, Glenat P. Topological modeling of methane hydrate crystallization from low to high water cut emulsion systems. Fluid Phase Equilib 2016;413:158.
10. Kim EJ, Kim JH, Kim M-S, Jeong SH, Choi DH. Process analytical technology tools for monitoring pharmaceutical unit operations: a control strategy for continuous Process verification. Pharmaceutics 2021;13:919.
11. Sirota E, Kwok T, Varsolona RJ, Whittaker A, Andreani T, Quirie S, Margelefsky E, Lamberto DJ. Crystallization process development for the final step of the biocatalytic synthesis of islatravir: comprehensive crystal engineering for a low-dose drug. Org Process Res Dev 2021;25:308.
12. Muhaimin M, Chaerunisaa AY, Bodmeier R. Real-time particle size analysis using focused beam reflectance measurement as a process analytical technology tool for continuous microencapsulation process. Sci Rep 2021;11:19390.
13. https://www.mt.com/int/en/home/products/L1_AutochemProducts/particle-size analyzers/particletrack-fbrm.html
14. Santos D, Maurício AC, Sencadas V, Santos JD, Fernandes MH, Gomes PS. Spray drying: an overview. In

biomaterials: physics and chemistry—New Edition; InTech: London, UK, 2018.
15. Gao Y, Zhang T, Ma Y, Xue F, Gao Z, Hou B, Gong J. Application of PAT-based feedback control approaches in pharmaceutical crystallization. Crystals 2021;11:221.
16. Gerzon G, Sheng Y, Kirkitadze M. Process Analytical Technologies - Advances in bioprocess integration and future perspectives. J Pharm Biomed Anal 2021;207:114379.
17. Su W, Hao H, Barrett M, Glennon B. The impact of operating parameters on the polymorphic transformation of D-mannitol characterized in situ with Raman spectroscopy, FBRM, and PVM. Org Process Res Dev 2010;14:1432.
18. Liu W, Wei H, Zhao J, Black S, Sun C. Investigation into the cooling crystallization and transformations of carbamazepine using in situ FBRM and PVM. Org Process Res Dev 2013;17:1406.
19. Nikita S, Mishra S, Gupta K, Runkana V, Gomes J, Rathote AS. Advances in bioreactor control for production of biotherapeutic products. Biotechnol Bioeng 2023;120:1189.
20. Gillespie C, Wasalathanthri DP, Ritz DB, Zhou G, Davis KA, Wucherpfennig T, Hazelwood N. Systematic assessment of process analytical technologies for biologics. Biotechnol Bioeng 2022;119:423.
21. Butler HJ, Ashton L, Bird B, Cinque G, Curtis K, Dorney J, Esmonde-White K, Fullwood NJ, Garden B, Martin-Hirsch PL, Walsh MJ, McAinsh MR, Stone N, Martin FL. Using Raman spectroscopy to characterize biological materials'. Nature Protocols 2016;11:664.
22. Silge A, Weber K, Cialla-May D, Müller-Bötticher L, Fischer D, Popp J. Trends in pharmaceutical analysis and quality control by modern Raman spectroscopic techniques. Trends in Analytical Chemistry 2022;153:116623.
23. Walla B, Bischoff D, Viramontes IC, Figueredo SM, Weuster-Botz D, Recent advances in the monitoring of protein crystallization processes in downstream processing. Crystals 2023;13:773.
24. Talicska CN, O'Connell EC, Ward HW, Diaz AR, Harding MA, Foley DA, Connolly D, Girard KP, Ljubicic T. Process analytical technology (PAT): applications to flow processes for active pharmaceutical ingredient (API) development. React Chem Eng 2022;7:1419.
25. Miyai Y, Formosa A, Armstrong C, Marquardt B, Rogers L, Roper T. PAT Implementation on a mobile continuous pharmaceutical manufacturing system: real-time process monitoring with in-line FTIR and Raman Spectroscopy. Org Process Res Dev 2021;25:2707.