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Current Industry Perspective on Process Analytical Technique Tools and their Recent Development in Pharmaceutical Oral Solid Dosage Formulations

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Abstract

Current review offers extensive understanding and implementation of process analytical technology (PAT) tools in manufacturing of pharmaceutical oral solid dosage (OSD) forms to streamline product's time to reach to market and increase profitability. PAT tools provide OSD formulators with an in-depth process understanding that supports accurate and responsive in-line control across all the unit operation, starting from input of raw materials to the delivery of end products. Data collected by PAT tools can be used for improving process understanding and better process control. Recent developments and application of PAT tools in OSD with current industry perspective is an emerging topic over a past decade attracting both academic and industrial researchers. In this review, we covered application of PAT tools in pharmaceutical OSD unit operations (such as blending, granulation, tableting and coating), PAT concepts, PAT tools for OSD, regulatory view, recent developments and application in pharmaceutical industry. By examining current challenges and recent advancements, this review makes a substantial contribution to the evolving field of pharmaceutical manufacturing, bridging key gaps in the existing literature and offering well-founded insights to guide future research and practical applications in the industry.

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Introduction

Process Analytical Technology (PAT) is a framework introduced by the U.S. Food and Drug Administration (FDA) under the initiative pharmaceutical cGMPs for the 21st century, a risk-based approach. It aims to design, analyze, and control pharmaceutical manufacturing processes through timely, in-process measurements of critical quality and performance attributes of raw materials, intermediates, and finished products (Calhan et al., 2017). This paradigm shift toward real-time quality assurance aligns with the Quality by Design (QbD) philosophy, emphasizing that product quality should be built into the process rather than tested into the final product (Kamble et al., 2013).

PAT employs a multidisciplinary approach, integrating physical, chemical, microbiological, mathematical, and statistical tools to enhance process understanding, control, and efficiency. The implementation of PAT in pharmaceutical oral solid dosage (OSD) manufacturing has significantly transformed traditional batch processes by enabling real-time monitoring and control, reducing variability, and improving product quality (Rathore et al., 2010). PAT tools are increasingly used to identify and control critical process parameters (CPPs) and monitor critical quality attributes (CQAs) across key unit operations such as blending, granulation, tableting, and coating.

Recent technological advancements including developments in spectroscopic methods (e.g., NIR, Raman), imaging systems (e.g., Eyecon, OCT), and data interpretation tools (e.g., chemometrics, model predictive control) have expanded the capabilities of PAT, making it an integral part of modern pharmaceutical manufacturing (Singh et al., 2014). These tools not only support enhanced process understanding but also contribute to faster decision-making, reduced production timelines, and minimized material wastage (Kim et al., 2014 and Chanda et al., 2015).

This review aims to provide a comprehensive overview of the current industry perspective on PAT tools and their evolving role in OSD formulation and manufacturing. It highlights regulatory insights, the application of PAT across unit operations, recent innovations, and the associated challenges. By consolidating current knowledge and practices, this review serves as a valuable resource for researchers and industry professionals working toward efficient, robust, and compliant pharmaceutical manufacturing.

PAT tools used in pharmaceutical oral solid dosage forms

Various strategies for integrating PAT tools into the Twin Screw Extruder (TSE) continuous manufacturing process are illustrated in the model shown in Figure 1. These approaches include: in-line analysis, where analytical tools are directly embedded within the process stream to enable real-time data acquisition; on-line analysis, which involves automated sampling from the process followed by immediate analysis using connected instruments; at-line analysis, where samples are manually collected and analyzed adjacent to the process to minimize result acquisition time; and off-line analysis, which entails manual sampling followed by transport to a separate laboratory for analysis. Each method plays a critical role in enhancing process understanding, control, and product quality within continuous pharmaceutical manufacturing.

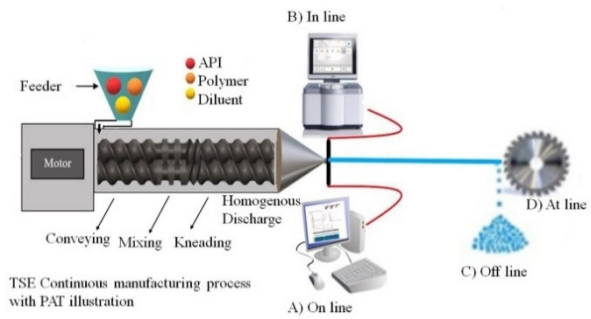

Figure 1: Various methods of implementing PAT tools into TSE Continuous manufacturing process. A) On-line analysis; B) In-line analysis; C) Off- line analysis; D) At-line analysis

Torque Monitoring System (TMS)

The granulation endpoint refers to the stage at which granules achieve optimal properties such as strength, bulk density, particle size distribution, and flowability, necessary for successful compression and the production of tablets with consistent quality. In a Rapid Mixer Granulator (RMG), the process typically involves three main steps: dry mixing, binder addition (often via spraying), and wet mixing or kneading. Key process variables such as the method of binder addition, impeller speed, and chopper speed significantly influence the final characteristics of the granules.

During the wet mixing phase, the resistance encountered by the impeller reflected by the current drawn by the motor serves as a valuable indicator for determining the granulation endpoint (Bouwman et al., 2005). A Torque Monitoring System sensor mounted directly on the impeller shaft (**Figure 2**), enables precise measurement of this resistance. Unlike indirect or theoretical methods (Manual / Visual inspection and Power consumption), this direct torque measurement provides greater accuracy and reliability, as it minimizes the impact of equipment wear and mechanical variability.

Figure 2: Illustrating the Torque Monitoring System sensor mounted directly on the impeller shaft of a rapid mixer granulator.

Torque sensors operate using strain gauges mounted on rotating components. This is typically achieved through the integration of slip rings, wireless telemetry systems, or rotary transformers, which allow for the transmission of signals from moving parts. **Figure 3** illustrates the correlation between direct torque readings from the impeller and the corresponding impeller current in a rapid mixer granulator model. Granulation is a critical step in tablet manufacturing, and accurately determining its endpoint is essential for producing tablets with consistent and desired properties. While traditional methods are commonly used for endpoint detection, they often lack the precision required for reliable control. In contrast, the TMS offers a more accurate and dependable solution for determining the granulation endpoint in RMG processes, thereby enhancing product quality and process consistency.

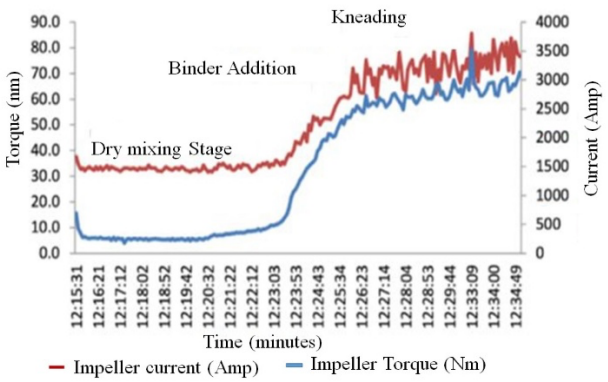

Figure 3: Correlation between direct impeller torque readings and the corresponding impeller current in a rapid mixer granulator model.

Near Infrared Spectroscopy (NIR)

Spectroscopy involves the study of how matter interacts with light and other forms of radiation, particularly how absorption and emission vary with wavelength. Near-Infrared Spectroscopy (NIR) is a molecular vibrational technique used to detect transitions in molecular vibrations. It can be performed using diffuse reflectance or transmission mode (Asachi et al., 2018). NIR spectroscopy has gained wide acceptance and adoption in the pharmaceutical industry for purposes such as raw

material identification, assay measurements across product development stages and monitoring and control of manufacturing processes (Sarker et al., 2006). Its key advantages include being fast, non-destructive, and requiring minimal or no sample preparation. It also supports qualitative and quantitative evaluation via multivariate analysis (Patel et al., 2017).

NIR Spectral range - as per ASTM, the NIR region spans 780–2526 nm (or 12820–3959 cm^{-1}). When NIR radiation interacts with a sample, it causes molecular vibrations and rotations depending on the chemical and physical nature of the sample. This produces a unique spectrum due to non-uniform absorption. Spectral data can be collected through reflectance, trans-reflectance, or transmission modes. Two major physical phenomena anharmonicity and Fermi resonance govern the characteristics of NIR absorption bands (Reich et al., 2005). *Figure 4* shows a NIR spectrometer setup used for online moisture content evaluation.

In NIR spectroscopy, spectral data are pre-processed and analysed using multivariate calibration models such as Principal Component Analysis (PCA) or Partial Least Squares (PLS) to extract quantitative or qualitative information about the sample. These models correlate spectral features with reference data, enabling prediction of parameters like moisture content or active ingredient concentration. In contrast, NIR chemical imaging combines spatial and spectral data to generate distribution maps of chemical components. These maps are created using advanced image processing techniques, including pixel-wise chemometric modelling, and may incorporate visual enhancements such as colour and contrast adjustments for interpretability. (Reich et al., 2005).

Regulatory View of NIR Spectroscopy

The FDA's guidance serves as a recommendation to support the development, validation, and application of NIR-based analytical procedures for assessing the identity, strength, quality, purity, and potency of drug substances and drug products. NIR-based process analysers can be employed for off-line, at-line, on-line, and in-line analysis to facilitate enhanced process understanding, monitoring, and control.

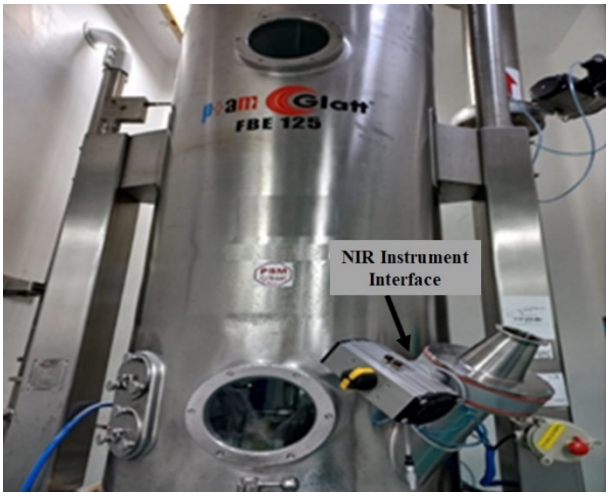

Figure 4: Illustration of the NIR Spectrometer setup utilised for on-line moisture content evaluation during the fluidized bed granulation or drying process.

Measurement, spectral acquisition time, sampling and sample preparation (In general, there is no need to additional process the sample for NIR analysis) should be considered while developing off-line or at-line measurements. However, if samples are prepared prior to spectral acquisition, the same sample preparation procedure must be consistently applied during calibration, validation, and routine prediction to ensure the accuracy and reliability of the NIR model.

The following factors during the development of on-line or in-line measurements should be considered such as interface, spectral acquisition, data collection, sampling and reference measurement - ideally, spectral acquisition and reference analysis should be performed on the same samples that will be used to develop the calibration model. It may be difficult, however, to use the same samples, particularly for in-line measurements. Therefore, when identical samples cannot be used, the pairing of spectra with the reference results should be justified.

Chemometric based NIR modelling to perform qualitative and quantitative analysis should involve construction of a calibration set, presentation of samples, development of chemometric models.

External Validation of NIR Analytical Procedures

As per FDA guidance, the external validation is different for different types of analytical modelling like qualitative, quantitative and rate of change procedures and should be validated as follows. Qualitative analytical procedures - specificity. Quantitative analytical procedures – accuracy, precision, specificity, linearity, range, detection and quantitation limits, robustness, rate-of-change procedures -to validate rate-of-change procedures, manufacturers should demonstrate both the adequacy of the NIR endpoint criteria and the specificity of the NIR procedure for components of interest. First, the adequacy of the endpoint criteria should be confirmed with an appropriate reference methodology. During the validation of the rate-of-change procedure, the procedure should be stopped as soon as the endpoint criteria are achieved; otherwise, misleading results may occur. Second, specificity can be demonstrated by showing that the wavelength region used for the NIR procedure included major bands of the components of interest.

Information to be submitted

As part of regulatory compliance, manufacturers are expected to submit detailed procedural documentation, including design and control strategies. Full development and validation reports for all NIR analytical procedures used in commercial production. A lifecycle maintenance plan, including calibration updates, model revalidations and software version control. All documentation must be readily available for inspection as part of the facility's quality system under ICH Q10 and FDA PAT/QbD initiatives.

Recent Industry Case Studies with NIR application

In recent times pharmaceutical industry adapted in application of PAT tool NIR for raw material verification, real-time blend uniformity (RBU) monitoring and moisture monitoring in granulation process are discussed in detail below.

a. Raw material verification (GMP-compliant) - A major pharmaceutical firm Abiogen Pharma S.p.A., Pisa, Italy, integrated NIR spectroscopy at the warehouse stage to verify raw materials. The non-destructive analysis allowed 100% identity verification without opening containers, improving GMP compliance and reducing contamination risks (Thermo Fisher, 2010).

b. Real-Time Blend Uniformity Monitoring - in a commercial tablet manufacturing line, a leading manufacturer Bayer AG, applied in-line NIR with chemometric modeling to monitor API-excipient homogeneity. The system reduced blending times by 25% and enabled real-time batch release, saving costs and time (Yusuf et al., 2009).

c. Moisture monitoring in granulation - using in-line NIR during high-shear wet granulation, GlaxoSmithKline (GSK) tracked moisture content in real time, replacing Loss on Drying (LOD) tests. This reduced process interruptions and material waste, while ensuring consistent granule quality (Yusuf et al., 2009).

Raman Spectroscopy

Raman spectroscopy is a non-destructive vibrational spectroscopic technique based on the Raman effect inelastic scattering of monochromatic light (typically from a laser) due to molecular vibrations. When incident light interacts with a sample, most scattering is elastic (Rayleigh), but a small fraction is inelastic, resulting in frequency shifts that reflect the chemical structure of the molecules (**Figure 5**). These shifts, known as stokes and anti-stokes scattering, provide a unique molecular fingerprint (Strachan et al., 2007; De Beer et al., 2011).

The technique uses laser illumination, a monochromator, and a detector, similar to NIR

instrumentation. However, raman scattering is inherently weak, and fluorescence interference can be a challenge. To address these limitations, advanced raman modalities have been developed as fourier transform raman (minimizes spectral interference), resonance raman (enhances signal intensity) and surface enhanced raman (increases sensitivity for trace detection) (Jesus et al., 2020). Raman spectroscopy is especially valuable in solid-state analysis, as water exhibits minimal raman scattering, making it suitable for formulations containing moisture.

Quantitative analysis and chemometrics - raman signals are proportional to analyte concentration, making the technique suitable for both qualitative and quantitative analysis. While univariate methods (e.g., peak height/area) are simple, overlapping spectral features often necessitate multivariate analysis as Principal Component Regression (PCR) and Partial Least Squares (PLS). PLS is particularly effective for real-time applications, as it maximizes covariance between spectral data and reference concentrations, handling complex, overlapping spectra (Jesus et al., 2020).

Real-Time Process Monitoring - In pharmaceutical manufacturing, raman spectroscopy is increasingly used for real-time monitoring and continued process verification (CPV) in unit operations such as blending, granulation, and tableting. It enables rapid assessment of API-excipient distribution, polymorphic transformations, moisture content and crystallinity. Compared to NIR, raman offers greater chemical specificity, while both techniques support fast, non-destructive in-line monitoring. The extensive spectral data generated from raman monitoring requires chemometric modeling to extract actionable insights, supporting enhanced process understanding and regulatory compliance under PAT and QbD frameworks.

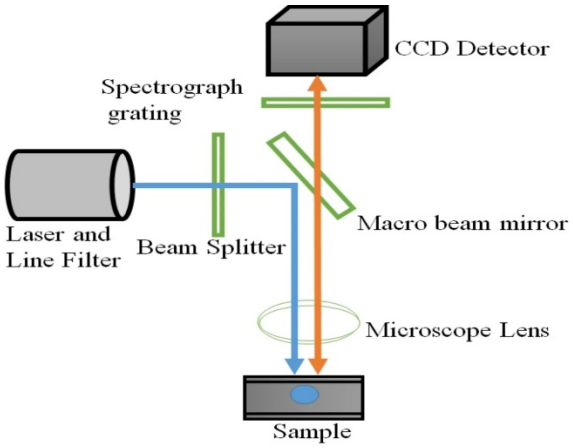

Figure 5: Schematic representation of working principle of raman spectrophotometer

2.4. Direct imaging particle analyzer (Eyecon)

A direct imaging particle analyzer is a non-destructive PAT tool used to measure particle size and shape within a range of 50 to 5500 μm. Eyecon, a type of direct imaging particle analyzer, captures images of both fluid and static materials and utilizes advanced image analysis to provide detailed information on particle size distribution and morphology (Naito et al., 1998). Eyecon supports both in-line and at-line modes of operation, enabling real-time or near-real-time monitoring of particle size and shape during pharmaceutical processes (Trivic et al., 2004; Palem et al., 2015).

Eyecon determines particle size distribution by analysing individual particle measurements within each captured image sample. Using intense pulses of light from a front-facing LED array, the system can image particles moving at speeds of up to 10 m/s without introducing motion artifacts. High-intensity LED pulses illuminate the sample every 0.65 seconds, enabling rapid, non-destructive analysis. The use of direct forward lighting improves the ability to distinguish overlapping particles. The camera sensor is synchronized with the LED pulses to ensure image capture occurs precisely during illumination. Captured images are processed by the EyePASS™ software, which applies advanced particle detection algorithms to identify and measure each particle. Eyecon

provides real-time data on particle size distribution, including D10 to D90 values in both numeric and volumetric formats, along with mean, median, live histograms, and S-curve representations. The D-values (e.g., D10, D25, D50) indicate the particle diameters below which a given percentage (10%, 25%, 50%) of the sample volume or number resides.

The D-values are determined by fitting individual particles with an ellipse, using an edge detection algorithm, in order to determine the minimum and maximum diameter of the particle, d_{min} and d_{max}. The magnitude of the 3rd dimension (d_{avrg}) is calculated by the average of d_{min} and d_{max}. The 3D volume of the fitted ellipse around any particle is calculated using Equation (1):

$$\boldsymbol{V = \frac{\pi}{6}\, X\, dmin\, X\, dmax\, X\, davrg} \qquad (1)$$

Eyecon reduces the time required to obtain representative measurements by capturing images of multi particulates and thus maximizing the number of particles captured per image. Eyecon has application in fluid bed coating, fluid bed granulation, milling, and twin-screw granulation. It can be used to reduce analytical time and increase process knowledge from development to commercial manufacturing. Eyecon provides the capability to either the formulation/process scientist or control system to stop the process based on a predetermined particle size. In-line and at-line modes of operation of Eyecon is presented as **Figure 6**. Limitations of Eyecon include its reliance on direct illumination for particle identification, which makes it unsuitable for accurately measuring transparent materials like glass or certain polymers. Additionally, highly reflective particles can pose challenges due to light reflections interfering with image capture.

Optical Coherence Tomography (OCT)

Optical coherence tomography is a non-destructive, high-resolution imaging technique based on low-coherence interferometry. It is increasingly being explored as a PAT tool for the real-time monitoring of film coating thickness and uniformity in pharmaceutical tablet manufacturing (**Figure 7**). OCT generates depth-resolved cross-sectional (2D) and volumetric (3D) images of semi-translucent materials by measuring the echo time delay of backscattered light from within the sample. Its high axial resolution (1–15 μm) makes it well-suited to detect fine surface features, coating layers, pores, and structural defects (Markl et al., 2014).

Figure 6: Eyecon2 in-line and at-line modes of operation (Kind permission from InnoGlobal technology)

While Terahertz Pulsed Imaging (TPI) also serves a similar role in measuring coating thickness, it operates at lower spatial resolution (transversal: ~50 μm; axial: ~40 μm), which may limit its precision for thin coatings ranging from 5 to 200 μm a common range in commercial tablets (Shen et al., 2011). In contrast, OCT offers superior axial resolution, making it more suitable for detailed analysis of thin and multi-layered coatings. OCT systems use low-coherence broadband light sources and interferometric detection to selectively image structures based on the delay in photon arrival time compared to a reference beam. This selective detection acts as a temporal filter, enhancing sensitivity to changes in coating thickness, density, and uniformity without the need for sample preparation. As a PAT tool, OCT provides valuable, real-time insight into coating quality, supporting process optimization and regulatory compliance under QbD and continuous manufacturing frameworks. Its integration into tablet coating lines offers potential for automated feedback control, contributing to consistent product performance and reduced manufacturing variability.

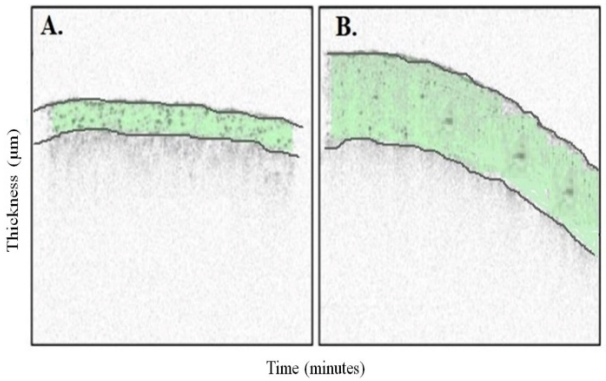

Figure 7: Demonstration of Optical Coherence Tomography images of in-house tablets acquired inline A). Eudragit based coating; (B) Cellulose acetate-based coating

Terahertz Pulse Imaging (TPI)

Terahertz Pulsed Imaging is a non-invasive, non-destructive imaging technique utilized in pharmaceutical manufacturing to monitor tablet surface characteristics and coating quality in real time. Operating in the terahertz region of the electromagnetic spectrum (between the mid-infrared and microwave regions), TPI provides unique spectral information linked to the crystalline structure of materials. Unlike mid-infrared (mid-IR) spectroscopy, which captures intramolecular vibrations and delivers molecular fingerprints, terahertz spectroscopy detects intermolecular vibrations, producing "crystal fingerprints." This makes TPI highly effective for differentiating between polymorphic forms or crystalline structures even when the molecular composition is identical (Shen et al., 2011). Terahertz radiation offers several advantages for pharmaceutical applications which includes, low scattering and minimal sample damage due to its longer wavelengths and lower photon energy compared to IR radiation, high sensitivity to layer interfaces, enabling precise measurement of coating thickness, density, and uniformity and real-time, in-line applicability, making TPI a promising PAT tool for continuous manufacturing. TPI's ability to penetrate excipients and resolve sub-surface features makes it particularly suitable for coating integrity assessments, layer delamination detection, and formulation monitoring during OSD production.

Focused Beam Reflectance Measurement (FBRM)

Focused Beam Reflectance Measurement is a real-time, in situ particle characterization technique that measures the chord length distribution of dispersed particles using backscattered laser light. A chord is defined as a straight line connecting two points on the boundary of a particle, and its distribution provides indirect yet valuable insight into particle size and shape (Kyoda et al., 2019). In FBRM, a rotating lens system directs a highly focused laser beam through a sapphire window, scanning in a circular path at constant speed. As the laser interacts with particles suspended in the focal zone, backscattered light is detected. The time delay between laser emission and the returned signal, combined with the scanning velocity, is used to calculate the chord lengths of the particles.

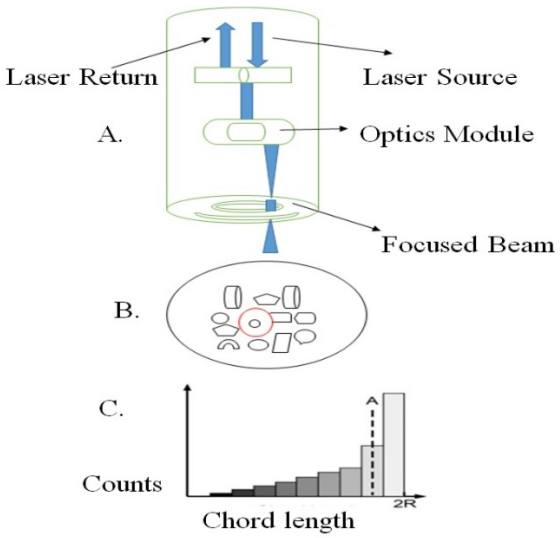

Figure 8: Illustration of working principle of Focused Beam Reflectance Measurement (FBRM) (A) FBRM probe design, (B) detection of particles by probe using a laser moving at a constant velocity, and (C) chord length distribution graph obtained from crystal distribution.

Key advantages of FBRM include no need for sample extraction or dilution, enabling direct, real-time monitoring of both dilute and concentrated systems. Rapid acquisition of thousands of chord

length measurements per second, producing statistically robust distributions. Sensitivity to dynamic changes, making it ideal for monitoring processes such as wet granulation, where particle growth, breakage, and aggregation occur.

FBRM is particularly useful during the granulation stage of OSD manufacturing to assess particle size distribution (PSD), shape evolution, and growth kinetics, all of which are critical quality attributes for downstream processes like drying and tableting. The working principle and setup of FBRM in pharmaceutical processes is illustrated in **Figure 8.**

Chemometric Tools

Data collected from spectroscopic and imaging tools often require advanced processing before they can be effectively used for qualitative and quantitative analysis. Chemometrics, which employs statistical and mathematical techniques, applies multivariate models to identify relationships between samples and variables, transforming complex data into latent variables. Multivariate data analysis focuses on interpreting datasets with multiple variables measured across numerous samples, aiming to capture and explain variations within the data matrix to extract meaningful insights. When integrated with PAT tools, chemometrics enhances the understanding of CPPs and their impact on CQAs, thereby enabling real-time process monitoring and control in pharmaceutical manufacturing (Challa et al., 2013; Kumar et al., 2014).

Chemometric methods involves regression methods such as multiple linear regression, principal component regression, and partial least squares and classification methods such as discriminant linear analysis, principal component analysis, and cluster analysis (Lopes et al., 2005).

Industry applications and recent development of PAT tools in oral solid dosage unit operations

Blending

Blending is an essential process for preparing all pharmaceutical formulations, including suspensions, emulsions, and injections, as well as oral solid dosage forms, such as powders, granules, tablets, and capsules (Palem et al., 2024). It is a process of mixing active pharmaceutical ingredients (APIs) and excipients to ensure a consistent mixing of all ingredients for each manufacturing process, can be performed multiple times during the manufacturing process when new excipients need to be added to the mix. Blending is a critical unit operation in pharmaceutical manufacturing, as achieving powder homogeneity is essential to ensure content uniformity in the final drug product. The blending process is influenced by various factors, including process parameters such as blender design, blending time, speed, and fill level (occupancy), as well as the physical properties of the ingredients such as particle size, shape, density and environmental conditions like temperature and relative humidity (Zhong. et al., 2020).

The selection of blending parameters largely depends on the characteristics of the materials being mixed and the geometry of the blender. Optimizing these parameters is crucial to achieving a uniform distribution of active pharmaceutical ingredients and excipients throughout the blend. The conventional approach to assessing pharmaceutical powder blending uniformity relies on wet chemistry assays, such as high-performance liquid chromatography. However, this method has several limitations, including reliance on thief sampling which is prone to sampling errors delayed process decisions, sample destruction, and being time-consuming and labor-intensive (Zhong et al., 2020). To address these challenges, spectroscopic techniques have been introduced for real-time monitoring of blend uniformity. Tools such as NIR and Raman spectroscopy offer non-destructive alternatives and can also be employed to investigate CPPs during blending.

NIR can be performed, with fibre-optic reflectance probes, to monitor the powder blending to minimizing assay time and sampling error (Reich G et al., 2005). Since most pharmaceutical active

ingredients and excipients absorb near-infrared radiation, NIR spectroscopy can provide valuable information on the homogeneity of all components within a blend. On-line NIR, when combined with techniques such as principal component score distance analysis (PC-SDA) and moving block standard deviation (MBSD), can be effectively used to determine the blending end point (Zhong et al., 2020). Additionally, in-line NIR allows real-time monitoring of excipient particle size distribution during the blending process. Partial least squares regression modeling has demonstrated a direct correlation between particle size and the NIR spectrum, enabling the identification of incomplete blending caused by undesired particle size variations. The application and industrial relevance of PAT tools in blending are summarized in Table 1.

Granulation

Granulation is a critical unit operation in the manufacturing of oral solid dosage forms in the pharmaceutical industry, aimed at addressing challenges related to powder handling, flowability, and uniformity. During this process, fine powder particles are agglomerated into larger, multiparticle entities known as granules, in which the individual components remain distinguishable. This increase in particle size enhances the bulk properties of the material. Granulation serves multiple purposes, including preventing segregation of formulation components, improving flow characteristics, and enhancing the compressibility of the powder blend for efficient tablet production (Burggraeve et al., 2013).

Granules have advantages like improved uniformity of the API in the final product, to better control in volumetric dispensing, less toxic exposure and process-related hazards (Jannat et al., 2016). Based on the type of bonding between primary particles granulation can be classified into two categories namely wet granulation and dry granulation.

Table 1: Application and industry perspective of PAT tools in different OSD unit operations

Unit Operation	CPPs	CQAs	PAT Tool	Measurement	Chemometric tool	Classification	Current industry perspective	Reference
Blending	Blending Time, Blending speed, Order of addition	Drug content & Blend uniformity	NIR spectroscopy	On- line, At-line	PLS / PCA /MBSD	Quantitative / Qualitative	Currently, industry is switching towards non-destructive method of analysis at blending stage as per FDA guidance. Few Organizations like Dr.Reddy's Labs; Torrent Pharma etc., have already started implementing at commercial stage.	Kim et al., 2014, Zhong et al.,2020, Palem et al., 2011
High Shear Granulation	Binder amount; binder concentration; binder addition time; kneading time	Granule size distribution; Granule Strength; Drug content uniformity; Density; Flowability	Raman Spectroscopy; Focused beam reflectance measurement; Torque Monitoring System	On- line, At-line; In-line;	End point indication algorithm;	Quantitative / Qualitative	Industry is looking for reliable option to help to overcome the endpoint determination in high shear granulation processes. Many industries like Dr.Reddys, Torrent etc., are exploring TMS & FBRM as an alternate option for granulation end point determination.	Kim et al., 2014, Agarwal et al., 2011
Low shear fluid bed granulation	Binder concentration; Spray rate; Atomization air pressure	Granule size distribution; Density; Flowability	NIR Spectroscopy; Eyecon	On-line, At-line; In-line	PLS / PCA / EyePASS ™	Quantitative / Qualitative	Industry looking for a control system to stop the process based on a predetermined particle size in low shear fluid bed	Kim et al., 2014, Trivic et al., 2004

Unit Operation	CPPs	CQAs	PAT Tool	Measurement	Chemometric tool	Classification	Current industry perspective	Reference
							granulation	
Roller Compaction	Roller pressure; Roller Speed; Roller gap; Feed rate; mill screen size	Ribbon density; Granule size distribution; Density; Flowability	NIR-Chemical Imaging; NIR Spectroscopy; Raman spectroscopy; Eyecon 3D imaging	In-line; On-line	PLS / PCA / EyePASS ™	Quantitative / Qualitative	Industry looking for online evaluation of the size, shape & physical properties of dry granulation	Rana et al., 2011, Vovko et al., 2020, Mcauliffe et al., 2015
Tableting process	Feeder speed; Pre-compression / main compression force; Dwell time; Ejection force	Tablet appearance; Thickness / dimensions Tablet porosity/density/solid fraction; Hardness	NIR-Chemical Imaging; NIR Spectroscopy;	In-line; On-line	PLS / PCA	Quantitative / Qualitative	Industry looking for online evaluation of the tablet porosity / density; thickness & hardness during compression unit operation.	Kim et al., 2014, Zhong et al., 2020, Khorasani et al., 2015, Bhowmik et al., 2014
Film Coating	Pan speed; Inlet air temperature; air volume; Spray rate; Atomization air pressure; curing time / temperature	Coating efficiency; percentage weight build up; coating thickness;	NIR Spectroscopy; OCT; Raman Spectroscopy; TPI;	In-line; On-line	PLS / PCA	Quantitative / Qualitative	Industry looking for online evaluation of the film coating thickness, desired weight build up & efficiency during film coating unit operation.	Kim et al., 2014, Zaid et al., 2020, Seo et al., 2020, Korasa et al., 2016
Wurster coating	Inlet air temperature; air volume (CFM); Spray rate; Atomization air pressure;	Film thickness, homogeneity, and roughness	OCT; TPI	In-line; On-line; Off-line	High resolution imaging	Quantitative / Qualitative	Industry looking for online evaluation of film homogeneity, roughness and thickness to control the desired release profile at different scales	Müller et al., 2012. Knop et al., 2013, Markl et al., 2015.

Wet granulation is a widely used technique in pharmaceutical manufacturing that involves the addition of a liquid either with or without a binder to a powder blend to form a wet mass, or alternatively, the simultaneous addition of powder and adhesive without compaction. This wet mass is then dried and subjected to size reduction to produce granules of the desired characteristics. The added liquid promotes particle agglomeration through capillary and viscous forces, which facilitate binding in the wet state. Upon drying, these temporary bonds are strengthened as solid bridges form through binder hardening and the crystallization of dissolved particles, resulting in stable granules (Agarwal et al., 2011; Rana et al., 2011). Uniform moisture content during the process is crucial, as it minimizes static charge buildup and ensures consistent granule quality. Common wet granulation methods include high-shear granulation and low-shear or fluid bed granulation, each offering specific advantages depending on the formulation and desired product attributes.

High shear granulators vigorously agitate the powder and simultaneous addition of binder to prepare granules. They are widely utilized due to their capability to process challenging feed formulations, including those containing high-viscosity binder solutions and fine, cohesive powders (Palem et al., 2016). In the high shear

granulator, the particles are set into movement by an impeller rotating at a high speed. Equipment also contains a chopper. Materials are mixed in the dry mixing phase, followed by addition of liquid and wet mixed to obtain granules with narrow particle size distribution. Thereafter, the granules are wet sieved, dried, milled and sieved again. The amount of liquid is critical in the granulation process, as it may lead to over-wetting. Variations in raw materials may affect the liquid requirement (Palem et al., 2012). Variations in the parameters like binder amount, binder concentration, binder solvent spray rate are affecting the quality attributes like granule size distribution, granule distribution, bulk density. In line FBRM can be used to measure the size and number of particles in real time. The Intermediate quality attributes like moisture content, temperature, and wetting can be monitored using Online Raman Spectroscopy (Kim et al., 2014). Granulation end point shall be monitored by TMS.

Low shear fluid bed granulation process involves the spraying of binder solution, suspension or dispersion onto a physical mixture of fine solids, where particles are suspended in air stream. These particles are wetted by a sprayed binder solution, and upon collision, liquid bridges form between them, initiating granule formation. These liquid bridges hold the particles together through surface tension at the liquid-solid interface or through capillary (hydrostatic) suction forces.

In general, Low shear fluid bed granular material is finer, free flowing and uniform. The fluid bed system operates by first heating the air, which is then passed through the material being processed. As the air flows through the product, it escapes through the void spaces within the material, facilitating efficient drying or granulation. A typical fluid bed system comprises several key components, including an air-handling unit, product container, air distributor, spray nozzle, disengagement zone, process filters, exhaust blower or fan, control system, and solution delivery system (Pawar et al., 2020). Variations in the manufacturing & process parameters like binder concentration, spray rate affects the quality attributes like bulk density, granule size distribution and shall be used appropriate PAT tools to control in process quality attributes. NIR Spectroscopy can be used to monitor the quality attributes such as moisture content, particle size, bulk density during the fluidized bed granulation process (Liu et al., 2017). Eyecon has application in fluid bed granulation to significantly reduce analytical time and increase process knowledge from development to commercial manufacturing. Eyecon provides the capability to either the formulation/process scientist or control system to stop the process based on a predetermined particle size (Trivic et al., 2004).

Dry Granulation

Dry granulation is the preferred method for granule preparation when the materials possess inherent binding or cohesive properties. It involves the formation of granules without the use of any liquids, relying instead on the compaction of powders to induce particle adhesion and agglomeration. In this process dry powder particles are converted to granules by compacting the particles to form flakes. Roller compactor method is one of the widely used dry granulation technique. In roller compaction, powder particles are consolidated and densified by passing the material between two high-pressure rollers, forming solid ribbons. These ribbons are then milled to produce granules of uniform size. As a dry granulation method, roller compaction is highly efficient and capable of processing large quantities of material within a short time. As a special sub-type briquetting utilizes special designed compaction rolls which divides the compacted powder in pieces (briquettes). Both raw material properties like particle size and morphology and process variables such as roll speed, feed screw speed, roll force etc., may affect the critical quality attributes such as ribbon density, porosity, drug content etc.

NIR spectroscopy has been employed to detect changes in compaction behavior and mechanical properties resulting from variations in ambient moisture content. Its broad applicability allows for the simultaneous assessment of critical quality

attributes of roller-compacted ribbons, including drug content, density, tensile strength, and Young's modulus (Vovko et al., 2020). MultiEye NIR system is a multipoint NIR spectrophotometer can be used for real time process monitoring and designed as a cost-effective instrument that can be used to achieve high signal to noise ratio. Using this NIR MultiEye system for inline monitoring has shown significant results for monitoring the ribbon envelope density when compared with the offline NIR technique (Mcauliffe et al., 2015).

NIR-Chemical Imagining spectroscopy along with chemometric tools such as PCA and PLS can be used to monitor the properties like Granule size distribution, ribbon porosity, Tablet tensile strength to deliver granules exhibiting robust tableting performance. PCA based model was developed along with the NIR-CI to map the ribbon porosity distribution and can be used to develop predictive model for granule size fractions. PLS based model was used to map and predict the API distribution and content (Khorasani et al., 2015). NIR-CI can also be used as complementary non-destructive tool to determine the ribbon density and map the density distribution across the width and along the length of the ribbons (Souihi et al., 2015). Offline Raman spectroscopy can be used to monitor the surface smoothness which is a direct indication of the crushing strength for the prepared compacts. In-line Eyecon particle imager captures the images of the particles and provides the shape and size information that allows the determination of particle size distribution (Mcauliffe et al., 2015).

Tableting

Tablet compression is a critical unit operation in oral solid dosage manufacturing, where powders or granules are compacted into tablets with high precision using a tablet press. The quality of tablets is evaluated based on appearance, assay, content uniformity, disintegration, and dissolution (Bhowmik et al., 2014). A key critical process parameter during this step is the compression force, which directly influences CQAs such as tablet hardness, content uniformity, and dissolution rate. Accurate control of this force is essential to ensure consistent tablet formation and performance. NIR-CI has emerged as a valuable PAT tool in this context. It enables the spatial mapping of compaction pressure distribution within tablets, offering insights into intra-tablet variability and its potential impact on CQA performance (Souihi et al., 2015; Palem et al., 2011). This helps manufacturers better understand the compression process and optimize settings for uniform product quality.

Coating

Film coating involves the application of a thin, uniform polymer-based layer onto tablets, capsules, pellets, or granules, primarily to modify drug release characteristics such as site, rate, and time (Zaid et al., 2020). Ensuring inter- and intra-batch coating uniformity is essential, as variability can lead to defects like logo bridging, cracking, mottling, and rough surfaces, often resulting from poorly optimized process parameters (e.g., spray rate, air flow, and curing time) (Seo et al., 2020). PAT tools in coating process categorised as Spectroscopic Monitoring of Coating Processes - NIR Spectroscopy, NIR is widely used for monitoring coating thickness, drug content, curing extent, and dissolution behaviour in real time. Coupled with Principal Component Analysis, NIR enables qualitative discrimination of coating mass across tablets during pan coating. Pre-processing techniques such as Standard Normal Variate and derivative transformations improve spectral clarity and reliability. Partial Least Squares (PLS) regression allows for quantitative predictions of coating attributes, including drug content, tablet hardness, and endpoint determination (Gendre et al., 2011). At-line NIR with PLS is used for monitoring functional coating layers, especially in Wurster coating processes (Naidu et al., 2017). Raman is less affected by moisture, making it suitable for real-time monitoring of multi-layer coatings, polymorphic changes, and coating thickness (Müller et al., 2012). Complementary to NIR, Raman can better assess coating uniformity in aqueous environments.

Imaging Techniques for Coating Analysis – TPI, a non-destructive, high-penetration imaging method to assess coating thickness and quality without requiring chemometric models. TPI can also predict dissolution performance of sustained-release formulations and evaluate coating uniformity in pan coating (Knop et al., 2013). Requires knowledge of the material's refractive index, typically obtained via terahertz transmission spectroscopy. OCT, a high-resolution, non-contact imaging technique suitable for monitoring film coatings during fluidized bed Wurster processes. OCT captures depth profiles, offering insights into coating thickness, homogeneity, and roughness without chemometric calibration (Markl et al., 2015). While OCT provides superior resolution, its limited penetration depth may restrict visualization of deeper layers compared to TPI (Seo et al., 2020).

PAT tools such as NIR, Raman, TPI, and OCT significantly enhance the understanding and control of film coating processes. Each technique offers distinct advantages in terms of resolution, depth penetration, and sensitivity to moisture allowing manufacturers to ensure consistent coating quality, predict drug release profiles, and reduce batch failures.

Future trends and challenges in PAT: practical implications for industry and academia

While PAT continues to revolutionize pharmaceutical manufacturing, its widespread adoption across the industry is still hindered by several critical challenges. Overcoming these barriers is essential to fully realize PAT's potential in enhancing product quality, enabling continuous manufacturing, and streamlining regulatory compliance. Comparative PAT tool practical implications for industry and academia are presented in Table 2.

Skill Gaps and Multidisciplinary Expertise - The effective deployment of PAT tools requires a unique blend of skills across multiple scientific and technical domains. Proficiency in spectroscopy, chemometrics, data analytics, process engineering, and pharmaceutical sciences is essential for interpreting complex multivariate data and translating it into actionable process insights. However, the current talent pool with integrated expertise across these areas is limited. Bridging this gap will require strategic investment in interdisciplinary training programs, collaborative education models, and stronger industry-academia partnerships to cultivate the next generation of PAT professionals.

Data Management and System Integration - PAT tools generate vast amounts of high-dimensional, real-time data. The management, processing, and interpretation of this data remain a major challenge, especially in environments lacking robust digital infrastructure. Seamless integration of PAT systems with process control platforms, manufacturing execution systems, and enterprise resource planning tools is critical for enabling real-time decision-making. Advanced data analytics platforms, secure data storage systems, and cloud-based computing solutions must be developed and standardized to fully support data-driven manufacturing environments.

Regulatory Frameworks and Standardization - Regulatory bodies such as the U.S. FDA, EMA, and ICH have expressed strong support for PAT implementation and continue to issue guidance encouraging its use. However, variability in regional regulations, lack of harmonized global standards, and uncertainties around validation protocols for chemometric models and in-line measurements can deter broader adoption. A more unified regulatory landscape, along with detailed guidelines on validation, lifecycle maintenance, and model updating procedures, is essential to build industry confidence and streamline regulatory submissions involving PAT-based approaches.

Innovation, Customization, and Future Technologies - The future of PAT lies in its integration with cutting-edge digital technologies. AI-driven predictive analytics, machine learning (ML), and digital twin models are poised to

redefine process control by enabling real-time predictions, anomaly detection, and self-correcting manufacturing systems. Additionally, the development of compact, cost-effective, and modular PAT tools tailored to specific unit operations and product types will make these technologies more accessible across various manufacturing scales. Innovations in hybrid analytical platforms combining spectroscopy, imaging, and sensor technologies will further enhance the resolution, speed, and scope of process monitoring.

Table 2: Comparative practical implications of PAT tools between industry and academia

Aspect	Industry	Academia
Primary Objective	Real-time quality assurance and process optimization	Innovation, education, and development of novel PAT methodologies
Process Understanding	Enhanced control over CPPs and CQAs for robust and consistent manufacturing	In-depth exploration of process mechanisms and variable interactions
Regulatory Alignment	Supports QbD and cGMP compliance; reduces regulatory risk	Contributes to regulatory science and development of harmonized standards
Efficiency Gains	Reduces batch failures, speeds up scale-up, and lowers production costs	Streamlines experimental research and accelerates translational applications
Technology Development	Drives adoption of AI, digital twins, and automated feedback control systems	Develops and tests emerging PAT technologies (e.g., advanced sensors, chemometric models)

Conclusions

The implementation of PAT is pivotal to developing robust pharmaceutical manufacturing processes that consistently deliver high-quality products. By enabling real-time monitoring and control of critical quality attributes, PAT tools offer a scientific, risk-based approach that complements or surpasses traditional laboratory testing methods. Through integration across various stages from early formulation to commercial production PAT enhances understanding of raw material variability, process dynamics, and their impact on product performance. This leads to greater process efficiency, product consistency, reduced waste, and overall cost savings. Despite these benefits, challenges remain particularly in building the multidisciplinary expertise required to deploy and interpret PAT data effectively. As the pharmaceutical industry advances toward continuous and data-driven manufacturing, skilled professionals with competencies in chemistry, process engineering, data science, and chemometrics are essential. Regulatory authorities like the FDA continue to support PAT adoption, emphasizing flexibility in its implementation. Importantly, adopting PAT for one product does not mandate universal application, allowing for case-specific innovation. Looking ahead, the successful integration of PAT will depend on harmonized regulatory frameworks, digital infrastructure development, and investments in workforce capabilities ultimately paving the way for smarter, more agile pharmaceutical manufacturing.

Authors contributions

All the authors contribute equally to the design, literature collection, manuscript compilation, revision, and editing of the review article in the realm of scientific writing.

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Conflict of interest

The authors declare no conflict of interest.

Declaration of generative AI and AI-assisted technologies in the writing process

The authors declare that no original scientific content was generated or substantively edited by the AI. An AI–based tools (ChatGPT) was used in few sections during the final stage of manuscript preparation (post-writing) and exclusively for linguistic refinement in the English language (ChatGPT).

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