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Granulation process analysis technologies and potential applications in traditional Chinese medicine

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Abstract

Pharmaceutical production is changing from batch production to continuous production, during which granulation is one of the most important unit operations. The quality of mass-produced products is traditionally guaranteed by conducting off-line testing, which cannot meet the demand of continuous production for real-time monitoring of critical process parameters and critical quality attributes (CQAs) of the pharmaceutical granulation technology. Since the U.S. Food and Drug Administration proposed process analytical technology (PAT) in 2004, many PAT tools have been developed to monitor the granulation process and provide information regarding the granulation operation conditions and endpoint determination. In this article, we review the recent research and application of two PAT modes in the granulation process, namely, single CQA and multi-CQA PAT, with the aim to provide references for comprehensively improving the technological level of the pharmaceutical granulation process. Furthermore, the potential applications in traditional Chinese Medicine are discussed.

Keywords: Critical process parameters, Critical quality attributes, Pharmaceutical granulation technology, Process analytical technology

Introduction

Granulation is one of the most important unit operations in the production of pharmaceutical dosages. Ideal particle characteristics in the pharmaceutical process include good fluidity, shape, porosity, density, content uniformity, narrow particle size distribution (PSD), compressibility, and appropriate moisture content and hardness. The critical quality attributes (CQAs) of the granulation process primarily include granule moisture content, particle size, and density, which affect particle fluidity, compressibility, and stability[1–2].

The primary purpose of any granulation technology is to produce granules with the required size, shape, and moisture content. However, the high-quality requirements in terms of the ideal properties of particles and the physical and chemical stability of drugs have brought many challenges to granulation technologies. Specifically, in the granulation of traditional Chinese medicine (TCM), most of the raw materials are TCM extract infusions with complex composition, easy hydroscopicity, large adhesiveness, and diverse physicochemical properties. Some drugs also contain raw medicinal powder with uneven particle size and density, poor mobility, and easy stratification. Conventional granulation processes are difficult to be directly applied in TCM granulation, and the preparation of granules of TCM must be based on their own physicochemical characteristics when selecting the appropriate granulation process and equipment. Traditional granulation quality monitoring and endpoint detection were indirect and off-line, however, the CQAs in the granulation process can be directly monitored in realtime using the process analytical technology (PAT) tool.

Off-line testing, which is commonly used in the quality control of the pharmaceutical manufacturing process applies to post-analysis, which cannot timely adjust the manufacturing process, and is not suitable for the quality control of the continuous process. In 2004, the U.S. Food and Drug Administration (FDA) issued an industry guide on PAT[3], in which PAT was defined as a system for designing, analyzing, and controlling pharmaceutical manufacturing by real-time analysis of the CQAs of raw materials, intermediates, and processes. In some cases, PAT can be used to enhance process control and ensure that the CQAs are within the appropriate ranges to ensure quality. In the PAT framework, these tools can be divided into five categories: multivariate design tools, data collection and analysis, process analyzers, process control tools, and continuous improvement and knowledge management tools[4]. PAT can be used to detect key quality and performance attributes, design, analyze, and control production, thus shortening the production cycle and ensuring the final product quality.

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A literature review was conducted to find all published systematic reviews on the research progress of analytical techniques in the granulation process. A comprehensive systematic literature search for assessment tools on PC will be conducted in the IEEE, PubMed, Wiley InterScience, SCImago, Elsevier, Springer, Web of Science, CNKI, and EMBASE electronic databases. The literature search (systematic and hand-search) covers the period from September 2004 to December 2020.

Granulation method

Granulation methods are mainly divided into two types, dry and wet. The main methods for forming agglomerated particles include bridging, sintering, chemical reaction, crystallization, and colloidal particle deposition. Furthermore, agglomerated particles can also be achieved by the adhesion and cohesion of high-viscosity adhesives. Method selection requires a thorough understanding of the properties of the drug, excipients, required fluidity, and release characteristics. Dry granulation promotes the agglomeration of dry powder particles by mechanical pressure, while wet granulation is the mixture of raw material powder and granulation solution to form wet matter and promote agglomeration. Among these two granulation technologies, wet granulation is the most widely used. Dry granulation is mainly roller compaction granulation[5–6], while wet granulation includes fluidized bed granulation (FBG)[7–9], high shear wet granulation (HSWG)[10–11], and twin-screw granulation (TSG)[12–13]. Shanmugam[14] summarized the recent progress in granulation technology and provided a schematic diagram of each granulation technology. A brief description of frequently used granulation techniques and their mechanisms are listed in Table 1.

Dry granulation

Dry granulation, with few unit operations, short time consumption, and no solvent evaporation drying steps, is suitable for moisture- and heat-sensitive active pharmaceuticals ingredients (APIs)[15].

Roller compaction granulation means that the powder mixture is compressed between two counter-rotating rollers from a dense belt press block, and then the belt is ground into granules through a screen, and the granules are further mixed with excipients to form a compressed or encapsulated mixture. The factors affecting the rolling process include the physical and mechanical properties of raw materials, such as particle size and morphology, as well as process variables, such as the feed screw speed, roll speed, roll force, roll gap, and roll surface, and the change in environmental moisture content[16]. These parameters will affect the drug strip CQAs, such as their density, porosity, strength, and drug content, thus affecting the particle CQAs (PSD, fluidity, content uniformity, and compressibility). Without PAT, these parameters cannot be determined in real-time. Near-infrared spectroscopy (NIRS), near-infrared chemical imaging (NIR-CI), microwave resonance technology (MRT), thermal effusivity, and various imaging techniques have been used in off-line, at-line, on-line, and in-line modes to predict the CQAs of rolled belts and subsequent manufactured granules and tablets. The common goal of all these technologies is to improve granulation process understanding and control, and increase the output of high-quality products[17].

Wet granulation

Fluidized bed granulation

Compared with other multi-stage wet granulation methods, for example, extrusion, high/low shear granulation,

Table 1

Brief description of frequently used granulation techniques and their mechanisms

Granulation methods	Granulation mechanisms
Roller compaction granulation	The raw material powder is continuously pressed into ribbon blocks by two opposite rotating rollers, and then crushed into particles by the crushing unit.
Fluidized bed granulation	The pharmaceutical powder remains suspended under the gas flow, and the liquid is injected into the fluidized chamber to coordinate the powder into a core, gradually forming particles.
High shear wet granulation	The shear force forms a liquid bridge between the powder and the granulation liquid, and when the liquid is dispersed into the moving powder mixture, the particles begin to grow and form.
Twin-screw granulation	Twin-screw granulation conveys the material to the mixing zone, kneads the raw material into lumps with or without the help of a specific adhesive in the formula, and then collects it into particles at the discharge point.
Pneumatic dry granulation	A roller press-binding airpower grading method is used to obtain particles
Reverse wet granulation	A binder solution is prepared, and then dry powder excipients are mixed in the granulator and added into the binder solution, or the drug is mixed with a binder to form drug-polymer/binder slurry as a granulation fluid, and then mixed with other dry excipients to form granules.
Steam granulation	Water steam is used as a binder instead of traditional liquid water as the granulation liquid.
Moisture-activated dry granulation	A very small amount of water is used to activate the binder and trigger agglomeration, divided into two steps: 1) wet aggregation of powder particles and 2) moisture and distribution.
Thermal adhesion granulation	A small amount of water is mixed with a solvent as a pelletizing liquid and heated to promote particle formation. The drying process is eliminated.
Melt granulation	Facilitates the agglomeration of powder particles using meltable binders.
Freeze granulation	Liquid mud or suspension droplets are sprayed into liquid nitrogen, then freeze-dried and foam dried, forming particles.
Foam granulation	Granulation of a liquid/water-based binder mixed with API powder in foam form.

API: Active pharmaceutical ingredient.

and rotary granulation, FBG, which can integrate the mixing, granulation, and drying processes into a dust-free process, has many technical advantages. The FBG process has good heat and mass transfer efficiency, which can improve the particle CQAs, such as fluidity, bulk density, uniformity, compressibility, and solubility, by spraying the adhesive solution on the fluidized powder particles. Therefore, to ensure the transportation of products of constant quality, it is necessary to monitor some CQAs in the FBG process[18]. Da Silva et al.[19], Chang et al.[20], and other researchers reviewed the main techniques for monitoring and controlling the FBG process fluidization state, particle size, and moisture, focusing on the recently reported methods and achievements of FBG, coating process monitoring, and control. In these aforementioned reviews, the applications of NIRS, focused beam reflectance measurement (FBRM), spatial filter velocity measurement (SFV), acoustic emission (AE) method, capacitance measurement, microwave resonance method, and spectroscopy in FBG process monitoring, are discussed in detail.

High shear wet granulation

HSWG uses shear force to cause the powder to form a liquid bridge between the powdered material and the granulation liquid *via* electrostatic forces or hydrogen bonds in the granulation liquid (pure water, starch paste, or polymer adhesive solution). As the liquid is dispersed into the moving powder mixture, the particles begin to grow, resulting in the formation of agglomerates. The process of particle growth is finally close to the dynamic equilibrium state, in which the granulation liquid becomes uniformly distributed in the whole product block. Depending on the properties of the material and the main process conditions, the "equilibrium" stage of wet agglomeration is reached in approximately 5 min. Beyond this endpoint, the continued addition of liquids and/or mixing will lead to the collapse of the liquid bridge, the collapse of wet materials, and eventually excessive granulation.

Hansuld and Briens[21] reviewed the application of HSWG in the pharmaceutical industry, which is always used to improve powder properties for downstream processes, such as tableting and coating. Granule growth, however, is difficult to predict because the process is sensitive to raw material properties and operating conditions. Regulators encourage using PAT tools to improve process understanding and quality monitoring on-line. The primary technologies for HSWG monitoring include NIRS, Raman spectroscopy (RS), capacitance measurement, microwave measurement, imaging, FBRM, SFV, stress, and vibration measurement, as well as AE.

Twin-screw granulation

TSG can be divided into dry, wet, and melt granulation[22]. TSG[23] conveys the material to the mixing zone, kneads the raw material into lumps with or without the help of a specific adhesive in the formula, and then collects it into particles at the discharge point. The kneading zone in the barrel can be adjusted at any position as needed to obtain particles suitable for post-granulation. The particles obtained using TSG can be directly used for further processing or reduced in size to obtain the desired particle size. TSG can reduce batch loss and production time, improve drug safety, production output, quality, and is especially suitable for heat-labile drugs. However, to develop a robust and repeatable continuous granulation process, extensive research must be carried out using PAT tools.

TSG process parameters include the screw and feed speed, L/S ratio (for wet granulation), screw configuration, barrel temperature, residence time, torque, and barrel filling. Many studies on TSG have demonstrated the importance of process and formulation variables in obtaining the required particles[24–27]. The PATs used for monitoring the TSG granulation mechanism listed by Seem et al.[28] include NIRS, RS, NIR chemical imaging, positive emission particle tracking, 3D shape characterization, and on-line size measurement.

Other recently developed granulation technologies

Limited research progress has been achieved in dry granulation technologies in recent years. Pneumatic dry granulation is a novel granulation method utilizing roll pressing and air classification. Wet granulation, however, has a wide range of applications. Many novel wet granulation technologies have been developed in recent years, such as reverse wet granulation, steam granulation and moisture-activated dry granulation which can be combined with a high shear mixer and sprayer, thermal adhesion granulation, and melt granulation which can be used in a high shear mixer and fluidized bed granulator, freeze granulation and foam granulation[14]. These newly developed granulation technologies are progressing and filling the shortcomings and gaps in the existing granulation technologies, providing new support for continuous pharmaceutical development.

PAT implementation in pharmaceutical granulation techniques

In recent years, a variety of PAT tools for quality monitoring and control of preparation products have been reviewed[29–30]. In the process of granulation, these PAT tools can be divided into single CQA monitoring and multi-CQA monitoring tools according to their application scope. PAT on-line monitoring will produce a large amount of data, so it is necessary to combine it with multivariable data processing technology to establish models to better understand and monitor the granulation process. Jang et al.[31] introduced a modeling method based on PAT, which uses real-time CQA monitoring in the granulation process to adjust the process parameters to obtain the designed particles, and shortens the time required to measure CQAs, so that a more efficient granulation process can be achieved.

PAT of single CQA monitoring

PSD is one of the most important characteristics of particles and a CQA in the granulation process, which affects particle fluidity and compressibility. The different particle sizes correspond to different particle volumes, which affect the quality and content uniformity of the final preparation[32]. Therefore, it is meaningful to monitor PSD in the granulation process. Laser diffraction[33] and dynamic image analysis (DIA)[34] are mature techniques for measuring particle PSD, whereas emerging technologies include FBRM[9,13,35–38], SFV[39–45], 3D color imaging method[46], photometric stereo imaging[47], and AE. As shown in Figure 1, FBRM uses backscattered light and

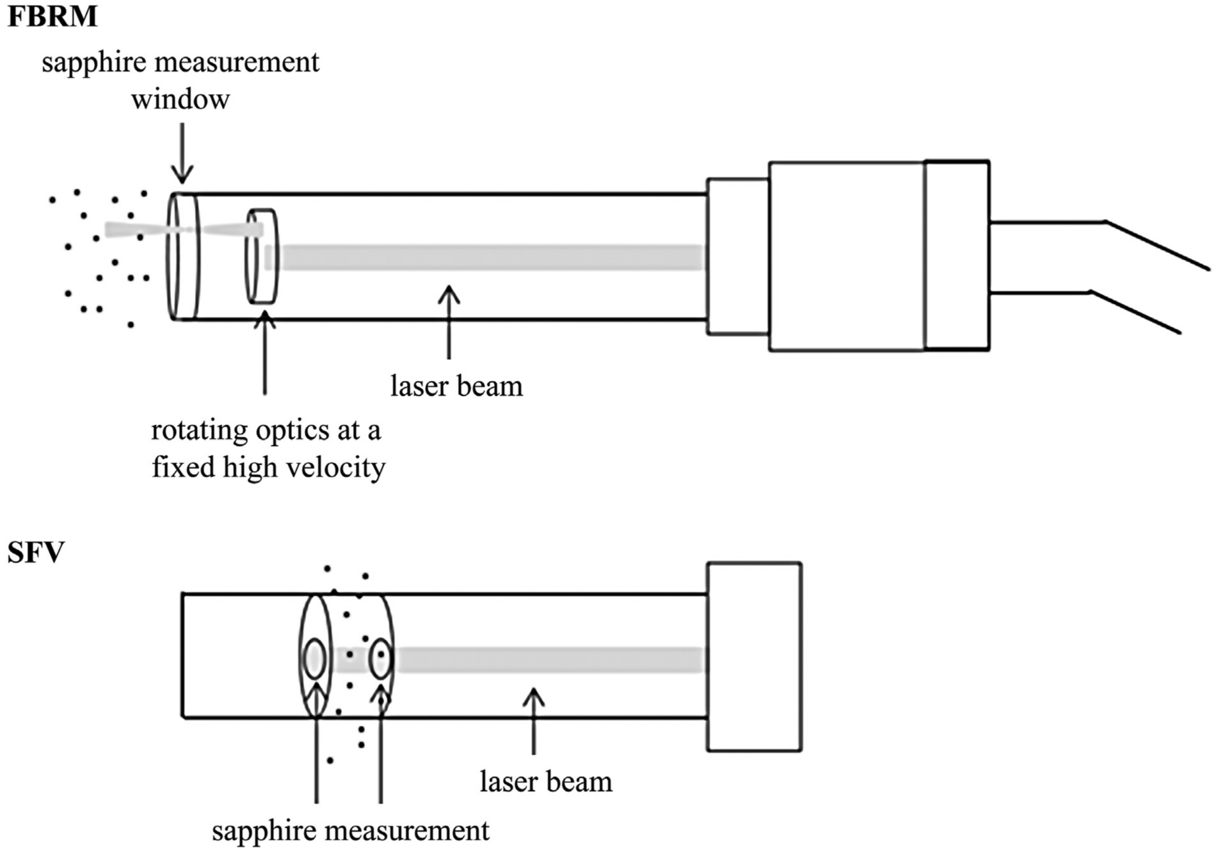

Figure 1. Schematic diagram of the FBRM and SFV techniques. FBRM: Focused beam reflectance measurement; SFV: Spatial filter velocity.

converts it to a dimensional measurement, while SFV uses the resulting shadows. PSD can be directly predicted using FBRM and SFV based on the principle of chord length distribution (CLD). FBRM and SFV are primarily used to measure the particle size in real-time, and to evaluate the factors influencing particle size and growth trends. Furthermore, the measurement analysis is fast and accurate. Imaging technology can provide intuitive information about particles, and it is easy to operate, repeatable, accurate and suitable for both dry and wet granulation. It can be used to measure the largest particles, to analyze parameters, such as the morphology of roundness and aspect ratio and to produce an intuitive and clear particle image. However, for the two PAT tools, the image of fine particles is not always very clear, and sometimes the error is serious.

SFV measurement

The SFV can simultaneously measure the particle size and velocity of the material flowing through a laser beam, thus creating shadows on the linear array of optical fibers[43,48]. SFV measurement is suitable for particle size measurements in the size range of 50–6,000 μm and particle velocity range of 0.01–50m/s, with a data rate of up to 20,000 particles per second. The measurement results are reported in a variety of ways, such as screening distribution (fraction, path), volume distribution, quantity distribution, and velocity distribution. Huang et al.[36] used an SFV-Parsum probe to monitor several granulation batches on a commercial scale FBG. A multivariate/batch statistical process control method was used to evaluate batch process performance, and differences between batches and to develop potential control strategies. The results showed that the measured values were in good agreement with the reference measurements of the off-line Malvern Master Sizer, indicating that the Parsum analyzer is a promising tool for on-line particle size characterization. Combined with multiple tools, the understanding of the FBG process can be improved. Reimers studied the feedback control system of the[44–45] FBG batch process PAT, using an improved time-based buffer system for realtime particle size measurement through in-line SFV to define the target particle size after spraying a specific amount of binder solution. After determining the appropriate control variables, the appropriate feedback control strategy was established, and then the control loop was adjusted to obtain the best performance of the integrated system. By adjusting the final target particle size within a specified range, the function of the system can be significantly improved. Furthermore, the implemented system can produce a predetermined target particle size by changing the process and formulation parameters.

Ismail et al.[49] developed a compartment population balance model to predict the PSD in a co-rotating TSG. The model is based on the liquid-solid ratio and screw speed, which represent the main process parameters of TSG. The mathematical model considers the aggregation and fracture of particles in the five compartments of TSG with a non-uniform screw structure.

Focused beam reflectance measurement

FBRM uses a laser beam to illuminate moving particles, which causes the laser to backscatter back to the probe, enabling the calculation of the particle chord length. FBRM is used as a PAT tool for on-line particle size analysis in continuous TSG[13] and HSWG[36]. The main purpose of the former is to evaluate the influence of process parameters on the correlation between CLD and PSD. The results were obtained when the screw and impeller speeds change in a certain range, and a significant relationship between CLD and PSD, can be observed. In the latter study, FBRM was used to study the effects of different amounts of water and wet coagulation times on the size and number of particles in the granulation process. In the process of adding water, the measurement of PSD was not ideal because of the noise caused by particle wetting/nucleation. An FBRM probe equipped with a mechanical scraper to avoid scaling was used to monitor the HSWG process[43]. Narang[50] used on-line FBRM- C35 probes to study the effects of formulation and process parameters on particle growth during HSWG of high drug loading brivanib alaninate formulations. The probe successfully monitored the change of particle chord length distribution with the granulation process and described the effect of water concentration in the granulation process.

Imaging

Imaging technology can provide intuitive information, such as particle size and shape information. Narvanen et al.[46] studied the feasibility of monitoring particle size using imaging technology. The particle surface was illuminated in three different directions, where red, green, and blue tricolor images were used to show the surface of the object, that is, the median trend of particle size in the FBG process. Therefore, a three-dimensional terrain image of the sample surface can be formed by digital images.

DIA and flash imaging technologies can provide particle size and shape information. DIA is a fast and non-invasive method, which can provide images of fast-moving particles and is sensitive to size and shape differences. Recently, it has been frequently used in the pharmaceutical industry to evaluate particle size and shape[51]. Hu et al.[35] realized the real-time feedback control of wet granulation using twin screws based on image analysis. Silva et al.[52] captured clear particle images with strong short light pulses, by illuminating the particles from different angles using various light-emitting diodes, and capturing the color of the surface in the image. Based on these data, surface height mapping is performed to obtain an image gradient, which is used to fit an ellipse on the edge of the particle, and the maximum and minimum diameters of the ellipse are further used to calculate the average aspect ratio.

Sandler[47] assessed the ability of DIA to determine appropriate particle sizes and shapes. They evaluated spherical and rod-shaped samples with a diameter meter and compared them with laser diffraction and scanning electron microscopy evaluations, respectively. The diameter meter has been used to determine the particle size and shape of powder particles[51,53] to predict their fluidity. Madarasz et al.[54] used the granulation of a mixture of lactose and starch as the model drug, developed a DIA-based particle size analyzer for continuous wet granulation to monitor and control the particle size in real-time, and successfully realized the monitoring and feedback control of the continuous twin-screw wet granulation process. Wilms et al.[55] used continuous sampling and DIA to measure the continuous on-line PSD, and different particle sizes were tested to determine the detection limit and the ability to immediately detect these changes and to develop a tool to control the PSD in the continuous granulation process.

Eyecon is a flash imaging technology based on digital size distribution, while Camsizer can use digital and volume-based dynamic imaging technology. The Eyecon high-speed imaging camera or Parsum probe can monitor the particle size and shape, whereas El Hagrasy can be used to monitor particle characteristics during fluidized bed coating and grinding. Mcauliffe et al.[56] used traditional sieving analysis methods and Camsizer and Eyecon 3D particle characterization devices to apply particle size measurement to the roller pressing process. The PSD trend results obtained using the three methods were highly similar, which indicated that there was good consistency between the traditional process control method sieving analysis and the new PSD measurement method. Eyecon and Camsizer show a significant prospect as on-line PAT tools.

Kumar et al.[57] evaluated the feasibility of implementing on-line particle imaging (Eyecon^{TM}) after continuous TSG and before the drying system. The off-line sieving method was used as the reference PSD analysis method, and the PSD of the particles leaving the TSG was measured on-line with the Eyecon^{TM} camera. The off-line measurement results were compared with the off-line measurement results obtained by screening the particle samples collected before and after the operation of the dryer. In the study of Sayin et al.[58], a real-time high-speed direct imaging Eyecon^{TM} system was used to analyze the particles made using twin screws, which could capture accurate PSD and particle counts. Then, the Shewhart control chart was used to evaluate the ability of the size parameters and particle count as appropriate control measures. Eyecon^{TM} can provide satisfactory on-line images, despite the dense flow of particles. However, before its application as a standard on-line particle size monitoring tool and control purposes can be realized, the analysis of these images is very important.

The photometric stereoscopic imaging technique combines the sample images irradiated by two different angle light sources to obtain the 3D surface images of the tested samples. The surface image is not only used to determine the PSD and shape but also provides information about the surface roughness. Sandler[47] demonstrated the application of photometric stereoscopic imaging to the on-line measurement of particle size and surface roughness in the process of granulation combined with automatic image processing algorithms. In addition, particle size determination was compared with that of the SFV and conventional sieving methods. Photometric stereoscopic imaging (Flash-sizer 3D) is also used to evaluate the PSD, roughness, and shape of wet particles in the study by Fonteyne et al[59].

Wilms et al.[60] used on-line laser diffraction to study and evaluate the effects of different process parameters, including residence time parameters and excipient formulations. The in-line and on-line laser diffraction data were compared with the off-line laser diffraction and DIA-data. The results show that the system can successfully monitor the PSD under various process and production parameters. The system is sensitive to changes in process parameters and material mixtures, which may pose a potential threat to the quality of the final drug products. The average propagation time from the compaction zone to the laser diffraction system is 17.7 seconds, indicating the system's fast reflection time.

Madarasz et al.[61] used a camera image-based mass flow measurement system and particle size analyzer for micro-feeding and measurement of powder, which can be used to carry out real-time mass flow and particle size monitoring as well as mass flow control. This video measurement system predicts the quality of the distributed powder with sufficient accuracy (the prediction error is 3.32% at 100 mg). Using the developed image analysis system and fishing scale to measure the mass flow at the same time, the ability of the video measurement system to monitor continuous micro-feed (0.2–1 g/min) is also tested, and the feedback control of the API micro-feed based on video quality flow measurement is realized. The quality prediction algorithm of the developed system can be further improved, and the video measurement method may modify or replace the weight supply method in a very low range of mass flow (less than 30 g/h). The video measurement system is also successfully applied to the on-line particle size analysis in the range of micro-feed, rendering the developed system a multi-functional PAT tool.

PAT for multi-CQA monitoring

NIRS, RS, and MRT can simultaneously monitor multiple granulation process properties. A review[62] introduced the basic principles of NIRS and RS and their applications in the on-line monitoring of the water content, PSD, API solid-state, and endpoint of the granulation process. Furthermore, spectral process fingerprints have been used to increase the understanding of the granulation process. Spectral imaging technology and some newly developed microwave resonance measurement technology and AE technology also play an important role in the multi-CQA monitoring of the granulation process.

Near-infrared spectroscopy

NIRS has become an important part of the US FDA PAT industry guide. Based on overtone and combinations of molecular vibrations of hydrogen bonds (C–H, N–H, and O–H), NIRS combined with a chemometric algorithm has become an extensively used tool due to its fast, nondestructive, and low-cost characteristics. In addition, due to the complexity of NIR spectral information, NIR spectral pretreatment is required, such as derivative, Savitzky-Golay smoothing, standard normal variate and multiplicative scatter correction.

The applications of NIRS in the monitoring of water content, PSD, and tablet/particle thickness in the CQAs FBG and coating process were reviewed by Liu[63]. Razuc et al.[64] summarized the application of NIRS in the determination of moisture content, particle size, bulk density, and coating in FBG. In this review, many spectra were provided to illustrate the basic principle of NIRS, and its application in monitoring mixing, pressing, and the coating was discussed.

Pauli et al.[65] used NIRS to monitor the PSD during continuous granulation and drying in real-time. Based on partial least squares regression (PLSR), three on-line NIRS methods were developed to predict the PSD of dried particles in continuous twin-screw wet granulation and the fluidized bed dryer (FBD) process. Using three independent on-line data sets, the applicability of the on-line process and its robustness to water contents and active drug components were further verified in real-time, exhibiting good consistency between the predicted and reference values. It has been proven that these methods can monitor the trend and sudden change of dried particles in the process of continuous granulation and drying. Because the NIRS method is highly productspecific, it is necessary to revalidate, adjust or even recalibrate it in the event of a formulation or product change.

Shibayama and Funatsu[66] studied the application of NIRS in vinyl amide granulation and coating steps to investigate which factors should be considered and solved in PAT model construction and management, and how to build a prediction model. The researchers built a model for the granulation step and verified the prediction ability of the model according to the external data set. According to the external verification, the PLSR model with manually selected wavelength had the best prediction accuracy for drying loss. It was found that the prediction of drying loss was accurate, but the prediction of particle size was not accurate enough.

Crowley et al.[67] studied how the variability of roll strip quality affected the NIRS detection results to monitor roll strip density, and proposed a simple method to eliminate outlier spectra. Gupta et al.[68] correlated the compaction strength and PSD with the slope of the best fitting curve for the samples prepared at different rolling speeds and feed rates using NIRS. The above relationship was found to be suitable for compacts prepared from microcrystalline cellulose powders and typical direct compression drug powder mixtures containing tomatine sodium dihydrate, microcrystalline cellulose, and calcium hydrogen phosphate dihydrate. The NIR spectra of the compacts prepared from the mixture of tomatine powder were also collected in real-time. The real-time slope of the spectrum was in good agreement with the off-line data. The strength of the compact was measured using the three-point beam bending method, and the PSD was determined using sieving analysis. The results showed that the real-time values of the best fitting line slope were reliable, which indicated that the proposed NIRS-based method was simple and fast, and that it can be used to monitor and control the production and magnification process of roll drying granulation.

Martinetz et al.[69] established the RTD model of residence time distribution of single unit operation (mixer, roller press, and tablet press) of continuous drying granulation and pressing line based on the NIRS. For semi-continuous bucket conveyors and pneumatic transportation, the assumption based on operating frequency is used. To verify the parameterized process model, the predicted API change and its propagation on the production line were calculated and compared with the multi-scale experimental operation of the production line with a fully assembled continuous operation. For the complete continuous dry granulation production line, this novel method showed satisfactory prediction ability under the selected mass flow rate. Furthermore, it demonstrated the function of process simulation as a tool to support the development and control of drug manufacturing.

Gavan et al.[70] studied an on-line NIRS method for monitoring the real-time moisture level in the granulation process. In the FBG process of two active drug components using the quality by design strategy, it was proven that the precise control of the key granulation parameters could reduce the variability of the input material. Although its spectral range is narrow, the microNIR spectrometer is successfully used as a powerful PAT tool. The results of the experimental design showed that the use of obviously interchangeable APIs and fillers in accordance with the pharmacopeia will lead to different final product key properties. By adjusting the CPPs (ie, adhesive injection rate and atomization pressure) as a function of material properties, the average particle size was within a narrow range of 280–320 microns, and the low ungraded part was less than 5%. Therefore, the precise control of the process parameters according to the particularity of the formula realized the maintenance of the product in the design space and eliminated material- related variability.

Chablani et al.[71] used real-time NIRS to determine the moisture contents of particles in the powder production process of a continuous twin-screw granulator-fluidized bed dryer. With the moisture contents determined with Karl-Fischer (KF) and loss on drying (LOD) as the reference values, the PLSR model of moisture contents was established, and the results showed that KF was a more suitable reference method than LOD. The experimental design of the central composite response surface was used to study the effects of inlet temperature and dew point on particle water content. It was found that the inlet temperature had a significant effect on the particle water contents measured using NIRS, KF, and LOD, while in the range of inlet air dew points studied, the effect was negligible.

Tian et al.[72] studied the quality consistency control of FBG by introducing a pulse spray and moisture content feedback control method and NIRS for the on-line quantitative analysis of CQAs, which was the particle CQAs. A self-tuning fuzzy PID controller was developed and applied to the FBG process. The performance of these strategies in quality consistency control was checked and similarity and principal component analysis (PCA) were used to evaluate the quality consistency of particles produced using these methods. The relative standard deviation of CQAs of particles produced using the pulse spray and moisture content control strategies was less than 5%, while that of conventional methods was more than 5%. The results showed that the moisture content feedback control strategy provides an effective method to improve the final particle quality, and simplifies quality consistency control by stabilizing important quality attributes. The boundary of the target product quality profile of some failure modes can be used to build an operation space for the granulation process. Another study by Tian et al.[73] carried out the process design and development of pulsed spray FBG using a laboratory-scale granulator.

Zhao et al.[74] used NIRS and multivariate process trajectories for the real-time monitoring and fault detection of pulsed spray FBG. Various types of multivariate statistical process control (MSPC) models (PCA, Hotelling-T^2, and DModX control charts) were developed to monitor batch changes throughout the granulation process. The results showed that the MSPC model based on NIRS includes the variability of the sample set that makes up the model, and can withstand external variability. This study proved that the combined application of synchronous NIRS and multivariable batch modeling is an attractive process monitoring tool and fault diagnosis method that can effectively control the pulsed spray FBG process.

PAT applied to process monitoring can generally provide multiple outputs coming from different sensors or different model outputs generated from a single multivariate sensor. De Oliveira et al.[75] contributed to the combination of sensor and/or model output to the current data fusion strategy in the development of the MSPC model. Data fusion was explored using three real process examples that uniquely combined multivariate model outputs from the same sensor or the combination of these outputs with other process variable sensors. The three examples studied demonstrated the benefits of flexibility in selecting model outputs, for example, prediction of key attributes using multivariate calibration, process profiles published from multiresolution methods, and the use of MSPC models based on fusion information, including model output and model output-based models. The original output of a single sensor was used for process control and the diagnosis and interpretation of abnormal process conditions. The proposed data fusion strategy is generally suitable for any analysis or biological analysis process that produces multiple sensors and/or model outputs.

Roman-Ospino et al.[76] evaluated three NIR probe interfaces for TSG based on the prediction performance of a multivariate analysis. A calibration model consistent with the change in API concentration was obtained from the data obtained through the second interface. The thin layer of powder between the screw and cylinder interface NIR sensor creates a sample presentation model, which can capture powder density information, thus, resulting in a calibration model with higher interpretation variance and lower prediction error. Although density affects prediction performance, the results showed that this important material property should be included in the calibration set to take advantage of the performance of the interface. The outlet interface combines the dynamics of the barrel interface and the large capacity of the rotary propeller interface. A steady flow of particles is produced on the vibrating surface, promoting the construction of a calibration model, which has an excellent performance in predicting low API concentrations in wet particles.

Avila et al.[77] tested the performance of low-cost NIR sensors based on the Fabry-Perot interferometer during FBG, including moisture monitoring, endpoint detection, and mass transfer monitoring process analysis. The spectral data and off-line water contents of 14 batches of fluidized bed desiccant particles were recorded. A PLSR-based moisture model was constructed to generate high-resolution moisture signals for endpoint measurement and mass transfer performance evaluation. The results showed that the sensor was robust to vibration and ambient temperature changes, and that the accuracy of water content prediction (±13%) was similar to that of the high-cost NIR sensor. The spectral quality and durability of micro-NIR sensors were sufficient for the construction of partial least squares (PLS) and MSPC models.

Roggo et al.[78] performed an on-line installation of three NIR probes from two different instruments to monitor the particles after the FBD in the continuous production line of solid preparations and the particles screened in the feed rack of the tablet machine, showing that the NIR probes can provide stable content uniformity results. After checking that all the IPC results were within the specification range, the PAT probe provided stable results, and no key changes were detected in the process parameters. In another study by Roggo et al.[79], the formula of the commercial entity was selected and NIRS combined with deep learning monitoring process parameters were used to predict quality attributes. The use of deep learning reduces noise and simplifies data interpretation to better understand the process. The synergy between PAT and process data processing technologies created a good monitoring framework for continuous production lines, increasing the understanding of continuous manufacturing lines.

Meng et al.[80] studied and compared three kinds of PAT tools, namely, Eyecon^{TM} 3D imaging systems, NIRS, and RS, in the process of continuous TSG, to realize real-time monitoring and prediction of CQAs of particles. The Thermo Scientific TM Pharma11 TSG was used to produce granules with anhydrous caffeine as a low-dose formula of the model drug. A full-factor design of 30 operations was carried out, including three CPPs (liquid-solid ratio, barrel temperature, and flux) to evaluate the performance of each analysis tool. Eyecon^{TM} successfully captured the particle size and shape changes from different experimental conditions and proved to be sensitive enough to the fluctuation of size parameter D10 in the presence of process disturbance. The PLSR model showed a relatively small relative standard error (less than 5%) of the predicted physical properties of most particles. On the contrary, the RS-based PLSR model showed a higher prediction error of particulate drug concentrations, due to the non-uniform premixing of raw materials during the development of the calibration model. Alcalà et al.[81] established qualitative and quantitative NIRS models, and monitored the relevant quality parameters of the formula, water content, PSD, and packing density.

Raman spectroscopy

RS is an optical vibrational technique based on the fundamental principle of inelastic light scattering. Compared with NIRS, RS is less affected by water. RS does not require sample pre-treatment, and is easy to operate with fast measurement speed and high sensitivity, but it is easily influenced by optical system parameters.

Nagy et al.[82] summarized the application of RS in granulation unit operation. RS can be used in the process of wet granulation to analyze the changes caused by water, but the application of RS in dry granulation was less. Mcauliffe et al.[56] detected the spectral differences related to the surface smoothness of tablets to analyze the mechanical strength of tablets prepared by rolling. In the NIRS analysis, when there is a large amount of water in the granulation process, the light absorption of water is too strong. Therefore, in this situation, RS is more suitable.

Fonteyne et al.[48,59] simultaneously used on-line NIRS and RS as well as a real-time particle size analyzer to evaluate the particle CQAs. NIRS is the most suitable method for monitoring the water content, and particle size analysis can be used to predict fluidity. RS is the most accurate method for monitoring hydrated hydration transformation in a theophylline-lactose model system.

Harting and Kleinebudde[83] carried out the first study on API content monitoring in twin-screw continuous granulation using an on-line Raman probe. RS has great potential in the analysis of the TSG process. The Raman probe can be inserted into a fluidized bed to analyze phase transitions, such as the hydration of risedronate[84].

Bhavana et al.[85] used RS, MIR, and NIRS combined with a PLS algorithm, to identify and quantify the crystal form of NHa in binary and multicomponent mixtures of niclosamide. It was found that compared with MIR, NIRS and RS are more accurate in identifying and quantifying NHa in binary and multi-component mixtures. In addition, these techniques allow the identification and quantification of NHa during ball milling and particle drying, and the results of NIRS and RS were comparable to those of MIR. However, RS can detect NHa in the presence of NHa, which is more effective.

Harting and Kleinebudde[86] optimized the measurement setting of the Raman probe to allow measurement in indoor light and further improve the prediction performance. Two different calibration models were developed and compared. For the first calibration model, the spectra was collected in the dark as before, and the second in indoor light. The dark calibration model could predict the API contents with a root mean square error of prediction (RMSEP) value of 0.31%, while the bright calibration model predicted an RMSEP value of 0.29%. Therefore, the two PLS models show prediction errors in the same order. The Raman spectra collected in indoor light can be, thus, evaluated. Furthermore, the previous prediction error of 0.60% can be significantly reduced. The optimized RS is suitable for evaluating the TSG mixing efficiency in the process of shunt feeding. The quality of the mixture is monitored behind different barrel parts using RS, and the corresponding API concentrations are predicted using the developed calibration model.

Reddy et al.[87] used on-line RS to monitor the multisolvent-induced changes of drug morphology during HSWG and drying, and investigated the effects of moisture, temperature, wet polymerization time, and drying process on drug conversion. A set of calibration standards was used to establish a quantitative PLSR model to predict the concentration of each drug during the process.

In the study of Otaki et al.[88] a low frequency (LF) RS (10–200 cm^{-1}) was used for *in situ* monitoring, and LF RS could obtain information about solid-state intermolecular and/or lattice vibration. The monitoring results obtained from furosemide/nicotinamide cocrystals showed that LF RS is an effective technique for *in situ* monitoring of suspension and FBG processes, and that it can be used as a PAT tool to detect the transformation risk of cocrystals. Furthermore, LF RS can be used to monitor the reaction, crystallization, and manufacturing process of APIs and products.

Based on the non-contact low-frequency Raman probe monitoring technology, Nomura et al.[89] used a variety of crystal planes and excipients to verify the crystallization state in the process of HSWG. The LF Raman probe showed comparatively high sensitivity in monitoring 5%–20% of two model drugs (acetaminophen and indomethacin) in a wet mass. The results showed that the probe-type low-frequency RS can be successfully used to distinguish and monitor the crystallization state and potential crystal transformation risk of API in real-time in the process of HSWG.

Hisazumi and Kleinebudde[90] used RS to monitor the coating process of multilayer films on-line. Using PLS and MCR analysis, a calibration model for predicting film thickness by RS was established, and the coating thickness of different batches could be correctly predicted. It was found that the prediction result of MCR analysis is better than that of PLS analysis because MCR analysis can separate the spectrum of the mixture into the pure component spectra, which is more suitable for the development of a robust quantitative calibration model for the granular multilayer film coating process. It is obvious that the additional calibration batch data with various parameters affecting the Raman spectrum are added to the calibration to develop a more robust and reliable prediction model.

Spectral imaging technology

NIR-CI is a combination of traditional NIRS and digital imaging, and the collected NIR spectral information and spatial information can be compiled into images (Figure 2). NIR-CI provides qualitative and quantitative information on the chemical and physical properties of strips, such as band density, spatial porosity distribution, tensile strength, pressure spatial distribution visualization, API concentration and distribution, and the CQAs of subsequent particles and tablets. Therefore, more experimental inputs are needed to confirm the applicability of the actual formulation, as most studies have been conducted on abbreviated formulations. Because of the complexity of processes and data, statistical methods should also be studied to improve the process analyzer so that it is fast and accurate enough to allow real-time analysis and process monitoring on both pilot and industrial scales [91–92].

Infrared thermal imaging technology is a nondestructive and non-invasive technology, which can be used to obtain the surface temperature of products in real-time. The main source of infrared radiation is heat. A thermal imager can capture the thermal characteristics of products and transform the information for further data analysis. The relative density of rolled strips is one of the CQAs in the process of roller compaction, which determines the porosity and PSD. Yu et al.[93] used infrared thermal imaging technology to monitor and analyze the powder temperature distribution in the roller belt to indirectly monitor the roller pressure on the powder. The thermal imager can draw the powder temperature curve on-line, and the increase of roller force leads to the increase in the slope of the powder temperature curve. In addition, the off-line measurement of X-ray CT was used to verify the density distribution of the roller belt powder from feeding to compaction. The results of powder temperature distribution and density distribution were analyzed and used to identify the pressure zone of the non-roller. Wiedey and Kleinebudde analyzed the uniformity of the strip using X-ray microcomputer tomography. In other studies by Wiedey and Kleinebudde[94–95], infrared thermal imaging technology was used to measure the relative density of the rolled strip on-line. A correlation was observed between the measured belt temperature and the belt density, and the cooling rate after compaction could be used to determine the strip density. Interestingly, the thermal imaging images also reveal the temperature distribution in the glass ribbon, which can match the uniformity of the strip density distribution measured and analyzed using X-ray microcomputer tomography scanning[96]. This technique showed a short reaction time to process changes, and no temperature drift with time was detected in long-term experiments. This study proves the applicability of a thermal imaging camera as a PAT tool to determine the relative ribbon density.

Terahertz pulse imaging (TPI) is based on terahertz radiation, an electromagnetic wave with wavelengths ranging from 1 to 0.1 mm between the far-infrared and microwave regions (300 GHz–10 THz). Terahertz radiation has the ability to penetrate most drug excipients, and the refractive index reflects the changes in density and chemical composition. Terahertz radiation has a lower photon ionization energy, so its potential application in the safe characterization of the chemical and physical properties of granular materials has aroused increasing interest[97]. Zhang et al.[98] used TPI technology to monitor the volume density distribution of the rolled strip, and developed a calibration method, which can convert the refractive index measured using TPI into volume density. The density distributions determined using TPI and slicing methods were compared and it was found that the density distribution determined using TPI is in good agreement with that measured using the crosssection method, which indicated that TPI can be used to accurately determine the density distribution with the calibration models. Furthermore, it was found that TPI measurement was very sensitive to the chemical composition of the drug.

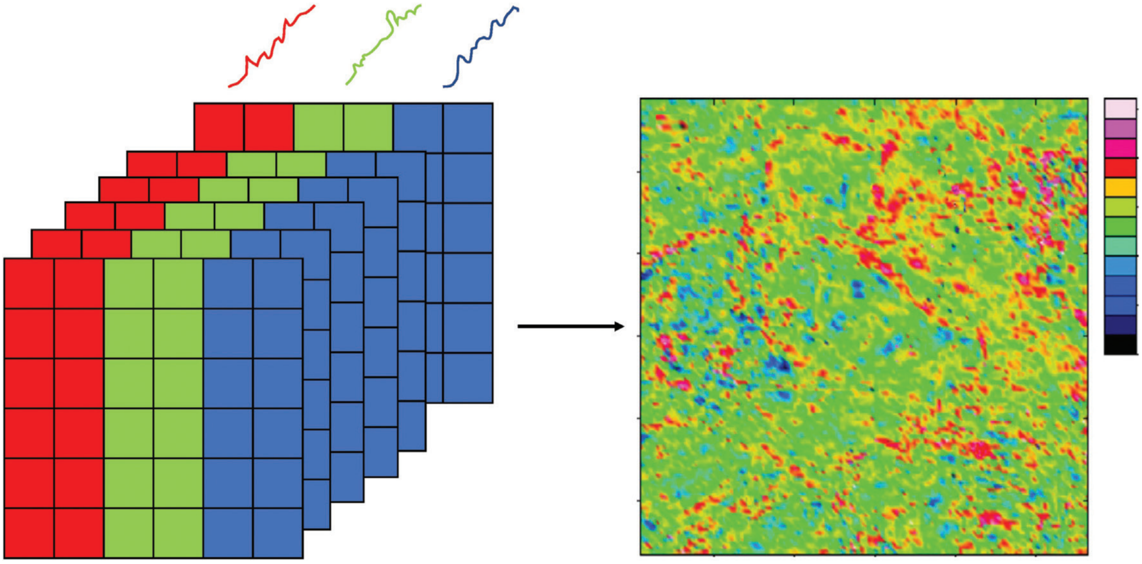

Figure 2. Three-dimensional matrix of Near-infrared chemical imaging (NIR-CI).

Wesholowski et al.[99] studied and tested the applicability of ColVisTec's UV/Vis spectrophotometer for the on-line determination of residence time distribution (RTD) in the hot-melt extrusion granulation process. Two different measuring positions in the co-rotating twinscrew extruder were compared with the off-line high-performance liquid chromatography-ultraviolet as the reference method, and the results were consistent, indicating that the on-line UV–Vis spectrophotometer was suitable for the determination of RTD in twinscrew extrusion granulation. Since the influence of measurement position on repeatability was found, it must be considered when PAT is implemented.

For continuous production, the quality of manufactured drugs should be evaluated in real-time. Sayin et al.[58] used complementary PAT tools to predict the quality properties of continuously produced particles. In their study, three PAT tools for real-time on-line analysis of particles produced by a continuous wet TSG in a powder-to-tablet production line (Consigma-25) were evaluated. RS and NIRS were used together with photometric imaging technology to obtain solid-state information and particle size data. These multivariate data were then used to predict the particle water contents, bulk densities, and fluidities. The three PAT tools evaluated in the Sayin et al. study provide supplementary information for predicting the quality properties of continuously produced particles. The residual water content was mainly related to the spectral data, and the imaging data had the highest ability to predict particle fluidity.

Acoustic emissions

Sound is defined as the generation, transmission, and reception of energy in the form of vibration waves, which can be used as the basis for the development of on-line monitoring and control systems. In the pharmaceutical industry, passive AE has been used to monitor HSWG and FBG processes and fluidized bed drying. Tsujimoto et al.[100] described that the generation of passive AE from fluidized beds was due to particle or particle device collisions, the friction of these collisions, and air turbulence generated by fluidized air. The main advantages of AE monitoring are the non-invasive and real-time collection of process information. It is a completely nondestructive indirect technology without any orifice or interface.

Poutiainen et al.[101] used the AE method to predict the PSD in the fluidized bed spray granulation process off-line. The acoustic spectra of 24 batches of the fluidized bed spray granulation process were recorded, and the acoustic data in the spraying stage were divided into different systems. Each system analyzed the acoustic spectrum using PLSR for different physical and chemical conditions at different stages of the process, and a prediction model for PSD was established. The results showed that the model had good PSD prediction accuracy and precision. In addition, the selection of AE technology as an early warning system to detect process deviation was evaluated. Although the accuracy of the PLS model can be greatly improved by three different modeling methods, AE technology was very sensitive to small disturbances, such as air turbulence, and was more suitable for stable granulation processes.

Hansuld et al.[102] demonstrated the relationship between audible acoustic emissions (AAEs) and particle size and density, and discussed the potential of on-line monitoring of product quality. The condenser microphone was placed in the exhaust pipe of a pma-10 HSWG to collect AAEs for experimental design. The particle size and density were changed by altering the Avicel grade in the formula. The results showed that the increase of particle size and density affected the decrease of AAEs observed at the end of granulation and during the process of overwetting. In addition, the change in particle size and density could be represented by different combinations of 10 Hz frequency groups, and the trend of multivariate scores supported on-line monitoring. Sheahan and Briens[103] studied the application of passive AE monitoring in particle coating in the fluidized bed. The microphone was connected to the top of the spray fluidized bed to reflect local fluidization conditions and nozzle performance information. The AE from the interface between liquid sprays and fluidizing granular beds determined the reduction of fluidization conditions, which affected the distribution of sprays in the whole bed and the drying of film coating around the core. The AE information obtained from the exhaust of the tower top outlet can be used to detect the nozzle blockage. Continuous research on the development of passive AE monitoring will provide important information on particle fluidized bed coating and may improve the process control for determining the optimal coating endpoint.

Watson et al.[104] developed a monitoring system that can identify different stages of the granulation process by combining a high-speed camera with AE to study the influence of process variables on granulation. This work showed that AE monitoring was beneficial to the monitoring of the wet granulation process. Although there was no clear link between particle size and adverse events, the AE can identify different stages of the granulation process. The combination of computational modeling and high-speed photography enables a better understanding of AE results. Through further modification and appropriate statistical analysis, the technology can be further developed into a more effective actual particle characteristic monitoring system.

Microwave resonance technology

MRT is a new method used to measure the physical properties of materials based on the interaction between water molecules and electromagnetic fields. Like NIRS[105], MRT can simultaneously monitor multiple CQAs in the granulation process. Austin et al.[5] found that the microwave sensor was very sensitive to water because the dielectric properties of water are very different from those of most solid materials. Therefore, microwave sensors can detect the concentration of water in the ppm range, whereas NIRS detection must use complex stoichiometric software and spectral pretreatment method to eliminate the physical influence in the spectra and to accurately monitor the chemical compositions. For MRT and NIRS data analysis, the ANN model is better than the PLSR model in water content prediction.

Peters et al.[106–110] developed a multi resonance microwave sensor, and carried out a series of laboratory and pilot scale-up studies, which could be used in the production of specific drugs (donepezil hydrochloride). Samples with different process parameters were used to establish a satisfactory moisture prediction model. The results showed that the sensor can be used as a tool to monitor the moisture contents of particles in the FBG

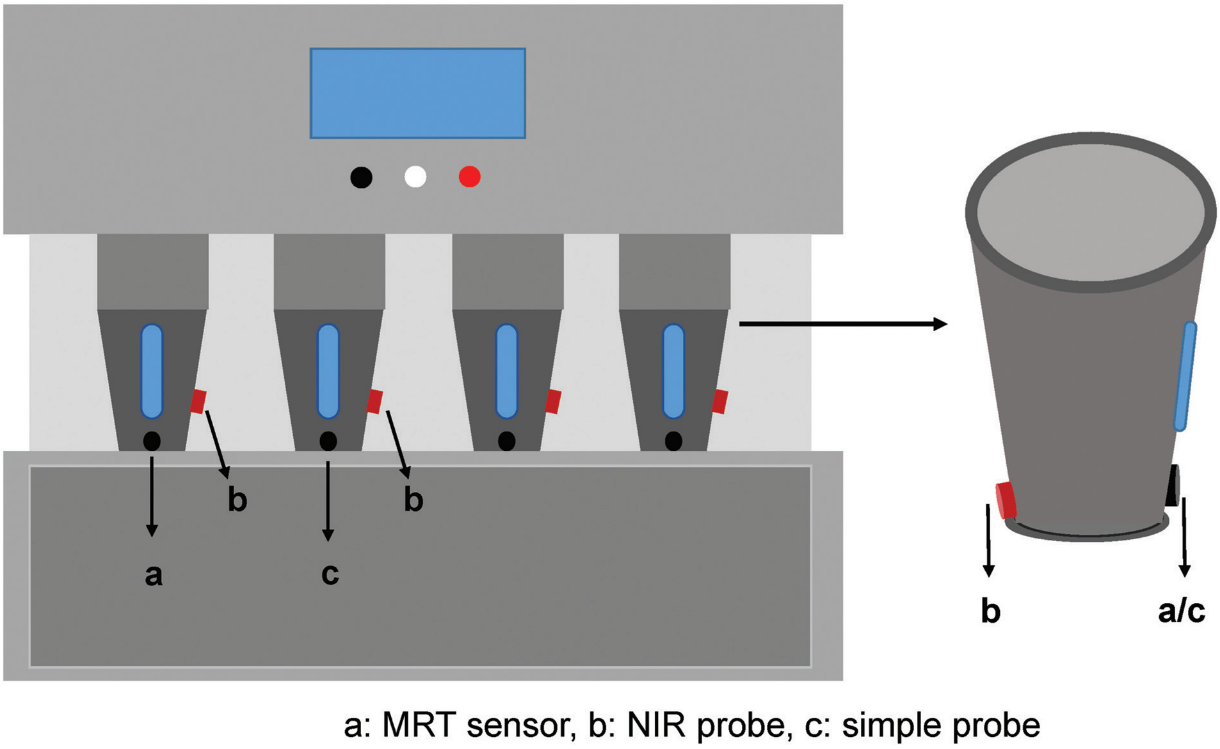

Figure 3. Real-time process monitoring device for semi-continuous fluidized bed drier using MRT and NIR. MRT: Microwave resonance technology; NIR: Near-infrared spectroscopy.

Figure 3 shows the real-time process monitoring of the semi-continuous fluidized bed dryer using MRT and NIRS. Due to the interaction between the water molecules and electromagnetic stray field on the surface of the MRT sensor, MRT is more sensitive to water than NIRS[109], which makes up for the limited applicability of NIRS in the analysis of the wet granulation process, such as colored particles, and large difference in bulk density[106].

In the pre-treatment of roller compaction, the powder mixture may segregate and cause quality deviation in the subsequent rolling operation, so it is very important to know the API concentrations in the roller belt. Gupta et al.[6] developed a new type of microwave sensor to measure the concentration of API in the roller tape on-line. The results showed that, compared with the commercial NIR probe, the microwave sensor has higher accuracy in the on-line monitoring of the content uniformity and density of the rolled tape. Similarly, as demonstrated in a study by Austin J et al.[5], in which the application of NIRS and MRT in monitoring the density and moisture of roller tapes was compared, microwave resonance had better accuracy, robustness, and ease of use in the measurement of properties compared with NIRS.

Other PAT technologies

Electrical capacitance tomography (ECT) is a type of electrical imaging method that uses the capacitance measurement of the object boundary and a mathematical algorithm to calculate the dielectric constant distribution inside the object. It is a non-invasive technology that can realize on-line monitoring. This method provides local point-by-point information from the target through the reconstructed sectional image, and the overall information can be provided by the feature metric calculated by the whole sectional image. This means that ECT can characterize the water contents and hydrodynamics of wet particles. Rimpilainen et al.[111] calculated the threedimensional water distribution based on the relationship between the experimentally-determined particle moisture and relative dielectric constant. The hydrodynamic properties of wet particles were characterized according to air velocity and particle moisture. Che et al.[112] used capacitance tomography to monitor the process of granulation and coating in a fluidized bed.

Thermal efficiency is a non-destructive measurement technology, which does not require intensive data preprocessing and chemometric data analysis for method development. Thermal efficiency combines the thermal conductivity, density and heat capacity of materials, and can distinguish the solid, liquid, and powder components in pharmaceutical preparations according to the heat transfer characteristics. The thermal conductivity of the powder depends on the ability to transfer heat through and between particles. Efficiency is also a function of the particle size, shape, density, and water content of the material. The sensor and the strip need to be contacted, and the air between them will affect the method, so it cannot monitor the long roll strip, and is only limited to the surface measurement, which needs to be developed[113].

The resistance flow force sensor drag flow force (DFF) is a hollow cylindrical pin with a diameter of approximately 1 mm. The deflection of the pin in the flow is measured by two optical strain gauges affixed to the inner surface of the pin. The sensor can measure information related to basic parameters, such as material density and shear viscosity. The DFF sensor can also output the temperature of the pin at a measuring rate of up to 500 samples per second. The local measurement of the flow force of the DFF sensor in the granulator has high robustness, sensitivity, and resolution. However, the real-time on-line evaluation of particle density remains challenging. In the study of Narang et al.[114] the resistance flow DFF sensor detected the wet mass concentration of particles in real-time, and the abilities of the FBRM and DFF sensors to monitor the granulation process were compared to evaluate the complementarity of the granulation process information from the two probes. At the same time, the particle size growth, densification, and DFF sensor response were measured. Furthermore, the application of the DFF sensor in granulation amplification was also studied. Narang et al.[115] used the DFF sensor to measure the flow resistance of three kinds of placebo formulations with different adhesive content during wet granulation, and compared the results with the data of particle properties collected at different processing times by the on-line FT4 powder rheometer. A good relationship was observed between the wet mass concentration measured using the DFF sensor and the flow resistance and interaction between particles measured using the FT4 powder rheometer. The force pulse amplitude measured using the DFF sensor could show the changes in material properties, such as shear viscosity and particle size/density, during granulation. These studies showed that the DFF sensor could be used as a valuable tool for wet granulation formulation, process development, and scale, as well as routine monitoring in the production process.

Potential applications in TCM

Granulation technology of TCM

Against the background of the modernization of TCM, the dosage forms of TCM are no longer limited to traditional decoction, pill, dispersant, ointment formulations, sublimed preparation, etc. New solid dosage forms such as granules, tablets, and capsules developed based on traditional decoction have become the main dosage forms in the current market, and the production of these dosage forms is inseparable from the granulation process. The resulting granules can be produced as final products or as intermediates in other dosage forms such as tablets and capsules[116].

At present, the common granulation methods in the TCM industry are dry granulation, spray drying granulation, and wet granulation such as extrusion granulation, FBG, and HSWG. TCM wet granulation technology has gradually matured, and dry granulation has also been gradually applied to TCM granulation production. However, compared with most chemical pharmaceuticals, these granulation methods face various intractable problems when applied to the production of raw materials' physicochemical properties, complex ingredients, and TCM[117–118].

Problems with granulation technology in TCM

Most of the raw materials used in the granulation of TCM are extract infusions, which have complex composition, easy moisture absorption and moisture absorption, large adhesiveness, and diverse properties, and some drugs also contain raw medicinal powder, which has some problems such as different particle size, uneven density, poor mobility, and easy stratification[119]. Therefore, many foreign novel granulation technologies are difficult to use directly in TCM granulation, and the preparation of TCM granules must be based on their own physicochemical characteristics to select suitable granulation technologies and equipment.

In wet granulation, because most of the TCM extracts have high viscosity, it tends to adhere to the inner walls and components of the equipment, blocking interfaces or sensors, making it difficult to clean, and, more importantly, the viscosity of the material is too high. Problems such as agglomeration, uneven distribution of material composition and particle size, can easily develop. After granulation, it is necessary to transfer and dry, which may lead to the risk of pollution. The granulation environment, with high humidity and high heat, is not suitable for TCM with damp-heat sensitive components.

The application of dry granulation in the granulation of TCM is more limited. The composition of TCM is complex, the material is viscous, and it is easy to absorb moisture. In dry granulation, a viscous wheel, viscous impulse, etc, may easily appear. The strip distribution is uneven, the delamination is serious, and the yield of primary granulation is low. For TCM powder with complex components, a large number of excipients and preparation processes need to be screened[120–122]. According to the characteristics of TCM, the dry granulation process is optimized. Then suitable dry granulation equipment is developed based on optimization, and then with the help of numerical simulation, the dry granulation process of TCM is studied[123].

Prospects for the application of PAT in TCM granulations

Currently, the production of solid formulations of TCM is shifting from traditional intermittent production to continuous and intelligent production[124–125] and continuous granulation is only one of the units. TCM granulation needs to solve many of the above-mentioned problems to achieve continuous production. The PAT listed in this paper has a potentially wide application in TCM granulation, and suitable PAT can monitor the CQAs of TCM raw materials and excipients as well as the CQAs of material particles during the granulation process in real-time, and provide real-time feedback to adjust the front-end steps, process and equipment parameters to ensure the quality of the final granules produced[126–127]. Liu et al.[128] established a PLS model through the combination of NIR and an automated control system to achieve on-line detection of several key indicators in the cold spirit concentration process in real-time automatic detection; Wang et al.[129] used AE detection technology to establish an AE prediction model of solid-phase particle size in cyclone separators, and the study showed that AE technology can achieve solid-phase particles. The study showed that AE technology can achieve accurate, non-invasive real-time on-line measurement of solid-phase particle size. The uneven quality of TCM raw materials and the lack of on-line control in the production process are important factors leading to the difference in the production quality of TCM granulation and TCM preparation. The application of PAT in the quality control of the TCM granulation process can realize “flexible manufacturing” and ensure product quality.

Conclusions

In the monitoring of the granulation process, novel methods such as AE and MRT are becoming important parts of PAT. Although the different PAT approaches are rapidly increasing, spectral techniques, such as NIRS and RS, are still the most widely used PAT tools in the granulation processes. Spectral technology and emerging microwave resonance and AE technologies can simultaneously monitor multiple CQAs, but the monitoring of these technologies requires the development of multiple models, which requires a lot of time and human resources. Unlike spectral techniques, SFV, FBRM, and imaging techniques do not require complex stoichiometric data analysis, and can directly measure the process parameters and CQAs of interest. The disadvantage is that their applicability is narrow and is usually designed to measure single attributes, such as particle size and moisture. The simultaneous application of multiple process analyzers is one of the solutions for comprehensive process monitoring and effective control of all key quality and performance attributes. In addition, due to a large number of granulation process parameters and material properties, when designing the process monitoring strategy, the process characteristics and process analysis capabilities of the different granulation technologies must be comprehensively considered. In conclusion, many process analyzers can be applied to the comprehensive design, analysis and control of the granulation process. Effective process monitoring combined with other PAT tools can be applied to comprehensively design, analyze and control the granulation process. However, as the existing methods still have many shortcomings and limitations, more research and development should be carried out in the future.

In recent years, the TCM granules and the dispensing granules of TCM have become more widely used in the clinic[130–132]. TCM granules are not only one of the commonly used dosage forms but also an important step in the preparation of oral solid preparations such as tablets and capsules. The TCM extract powder is obtained by extraction, concentration, drying, crushing, and other steps, in the molding process of granules for TCM. The hygroscopicity of the infused powder has a great influence on the molding of granules. The more adhesive, highly hygroscopic, and difficult to shape, in the granulation process, the more prone it to agglomerate or fine powder, resulting in poor granulation of the material, or even the failure of granulation[133–136]. Furthermore, all the types of granulation PAT tools mentioned above can greatly assist the manufacturing and development applications of TCM granules. A controllable granulation process will improve the physical and chemical attributes of TCM granules and yield better preparation. The PAT of granulation in the future will also be further improved to protect escorts for solid preparation of TCM development and modernization development of TCM.

Conflicts of interest statement

The authors declare no conflict of interest.

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Author contributions

Wenlong Li and Zheng Li project administration, fund acquisition, and conceptualization; Tongcan Cui writing original draft preparation; Tongcan Cui, Yizhe Hou, Huimin Feng, Sijun Wu, and Wenlong Li writing review and editing; all authors have read and agreed to the published version of the manuscript.

Ethical approval of studies and informed consent

Not applicable.

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