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Multi-sensors data fusion for monitoring of powdered and granule products: Current status and future perspectives

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ABSTRACT

Process Analytical Technology (PAT) is a systematic approach for monitoring of process parameters and product quality attributes and nowadays is considered for continuous processing of many industrial products. It is a mechanism to design, analyse and control manufacturing processes through on-line, in-line, at-line and off-line configurations for monitoring Critical Quality Attributes (CQAs). PAT systems include a combination of reliable in-line sensors, spectroscopic instruments and Multivariate Statistical Methods (MSMs) to provide informative knowledge for quality assessment of powdered and granule products. Nevertheless, monitoring programs of advanced manufacturing processes based on PAT systems typically provide large sets of data which are complex to interpret. The application of appropriate data-driven modelling techniques could assist in the interpretation of complex data matrices to better control of processes. Data fusion is a data-driven approach that could increase performance and robustness of models used for data interpretation to generate more accurate knowledge about process conditions and performance by merging related outputs collected from several instruments and considering synergies from multiple sources. This paper aims at presenting the current state of the art regarding the application of multi-sensors data fusion for powdered and granule manufacturing processes and making a critical review of recent progress and future possible perspectives in this field.

1. Introduction

Continuous processing of powdered and granule products comprising the integration of multiple unit operations in one production system is getting more attention due to advantages in improved productivity, product quality and financial services. While quality control and process performance in batch-scale production can be monitored through off-line measurements, in-process measurements become essential in a continuous manufacturing line [1–3]. The use of in-line PAT as an efficient process monitoring framework can help to meet not only Critical Quality Attributes (CQAs) for the desired products [4–6], but also could help in boosting quality assurance, product robustness, productivity and ultimately profits.

There are a number of key CQAs that must be checked through real-time monitoring in powdered and granule products, which bring in return significant impact on the quality of products as well as economics of the production. In many industrial sectors involved in manufacturing and handling of powdered and granule products, key CQAs include homogeneity in powder mixtures [7], particle size [8–10], powder flowability [11,12], moisture content [13–15], bulk density [9,16,17], particle strength and hardness [18–20], morphological forms [21,22], together with other quality attributes (Fig. 1).

For process monitoring in a continuous PAT manufacturing platform, the generation of increased amount of data can mainly be the consequence of installing multiple sensors continuously collecting information for prolonged periods of time. Gathering data from different sources could provide useful information about the process itself and the quality of final products, and yield better inferences in comparison to the use of an individual sensor. Nevertheless, this could significantly increase the complexity of data analysis and processing. In addition, some collected data may be uninformative and redundant due to the nature of the process,

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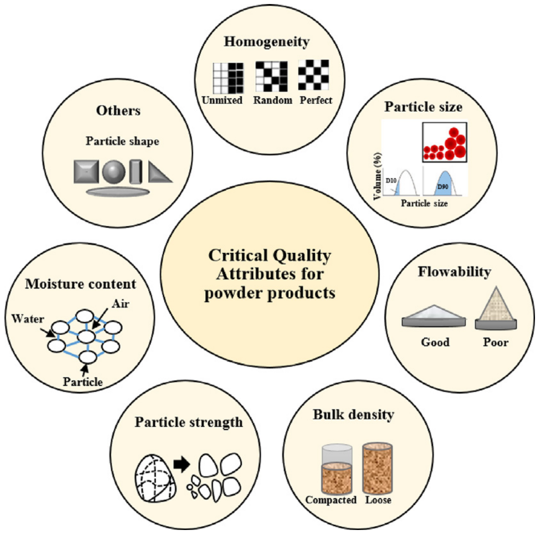

Fig. 1. Critical Quality Attributes (CQAs) for powdered and granule products.

limitation/fault in equipment, material type, and signal noises. By taking into account the growth in the size of data (multivariate datasets), velocity (fast/real time acquisition rate) and variety (multisource), advanced data analytics are recommended for the assessment of the big data [23,24]. In that sense, data fusion could be utilized in the field of PAT for an efficient handling of large analytical datasets in continuous processes. Implementation of an appropriate big data analysis strategy would be essential not only to eliminate the useless and redundant datasets, but also to integrate useful datasets in order to obtain a simple, consistent, accurate and useful interpretation of large and complex datasets.

Table 1 summarises the review papers that are available on the topic of data fusion for different applications. As it can be observed in Table 1, most of the review papers are relevant to food and beverage authentication, as well as analytical chemistry. However, a few review papers focus on manufacturing processes such as additive manufacturing, and pharma.

The use of multi-sensors and data fusion approaches has received attention mainly in the last decade for quality assessment of powdered and granule products. Nevertheless, the number of studies in this field is very limited, hence it is quite challenging to write a review on this subject. However, the authors believe that receiving the information of the current status and future perspectives on this theme is important for readers. Therefore, this paper aims to first provide an overview of the application of PAT for continuous manufacturing of powdered/granule products along with data processing, interpretation of PAT systems using a variety of Multivariate Statistical Methods (MSMs) and data fusion techniques. Then, the state-of-art PAT techniques used for the characterisation of product properties using single instruments and multi-sensor data fusion techniques are presented based on which further insights for creating complementarity of the data sets using data fusion approaches can be derived for powdered and granules products. Finally, the future perspectives of the applications of multi-sensors data fusion in PAT platforms for characterising a wide range of CQAs in continuous manufacturing of powdered and granule products are proposed by providing several examples.

2. Monitoring of powdered and granules materials using PAT tools

2.1. Objectives of a PAT framework

Handling (e.g. transporting, conveying, storing, dosing) of granular materials used for manufacturing of end particulate products is known to be challenging due to their complex material attributes which hinder an establishment of general constitutive equations relating shear rates and stresses [35,36]. The start-up efficiency of continuous powder processes is significantly lower than that of fluid processes. Powder processes often require ten times as much time to start-up as compared to fluid due to the

Table 1
The review papers available on the topic of data fusion.

	Domain	Objective	Main insight	Reference
1	Analytical Chemistry	Overview of data handling in data fusion; understanding of the data structure obtained from a particular instrument.	Knowing the structure of the data is essential to set the most adequate merging scenario for combining data.	[25]
2	Analytical Chemistry	Overview of the multi-block methods; tasks that can be performed with them and the pros and cons of different techniques.	Sensor/computing technologies can benefit from Multi-block data analysis to explore and combine data from multiple sources.	[26]
3	Analytical Chemistry	Overview of pre-processing techniques available for the application of multi-block methods; dealing with blocks that have data with different scales, and sizes.	Sensory data collectors placed at different points of the process need the selection of the appropriate pre-processing before modelling.	[27]
4	Analytical Chemistry	Overview of new data pre-processing trends based on ensemble of several pre-processing techniques.	Using multiple pre-processing can remove the artefacts (unwanted variation) that could be left behind by using only one technique.	[28]
5	Food	Overview of the applications of data fusion for food quality authentication; summarizing the tools, data processing algorithms, and fusion strategies.	Potential of advanced technologies for information fusion can be evaluated for comprehensive analysis of food properties.	[29]
6	Food and beverage	A general overview of data fusion strategies used in the field of food and beverage authentication.	Reliable sensor, and spectroscopic tools together with multivariate chemometrics could offer better results for food samples.	[30]
7	Animal source food	Overview of several achievements in the field of artificial sensors for the evaluation of animal source food products.	Employment of just a single sensor is often insufficient, and the use of multivariate methods is recommended for the quality assessment of food products.	[31]
8	Food	Overview of several achievements in the field of artificial sensors for the evaluation of food products.	Utilization of several instruments could provide better performance than the individual sources for processed foods and other edible products.	[32]
9	Manufacturing process	Overview of multisensory measurement systems and data fusion technologies and their applications in manufacturing systems such as additive manufacturing.	Multisensory monitoring and data fusion could offer complementary, and low cost analysis in the fields of industrial robotics and intelligent manufacturing.	[33]
10	Pharma	Overview of implementing data fusion in data types available for pharmaceutical manufacturing.	Data fusion techniques combined with machine learning can tremendously support the decision-making in Pharma 4.0.	[34]

adverse impact of powder inhomogeneity, powder transport problems due to poor flowability and improper degree of size reduction or enlargement.

In general, process monitoring can be achieved using different approaches (at-line, off-line, on-line and in-line configurations), (Fig. 2). For instance, at-line analytical techniques include the collection of a grab sample and its isolation from the actual process environment for the analysis of key required properties in close proximity to the process stream, while off-line analyses require that collected samples to be removed from the process stream and transported to a laboratory for further analysis [9,37]. The main difference between at-line and off-line analytical techniques is the time spent in the analysis. Usually, at-line analysis can be performed much faster than off-line analysis since a dedicated device is placed close to the production line to analyse product samples. However, traditional procedures using off-line and at-line analysers are discontinuous, slow and time-consuming and must be performed in a controlled location by highly trained technical personnel.

Real-time measurement data from state-of-art instruments could be alternatively used to monitor CQAs and performance properties of process materials and assist in the design, scale up and control of manufacturing processes. Real-time monitoring of the product quality will become the norm, as the powder manufacturing sectors including pharmaceutical industries are fast moving from batch to continuous processing. In recent years, in-line and on-line analytical techniques have been extensively used to obtain in-situ and real-time information on the state of the manufacturing process [9,37]. The desired characteristics of materials could be determined by transferring collected samples from the process line to the measurement device and returning it back to the process stream. This is the basis of on-line analytical techniques. On the other hand, in-line analysers that may be intrusive or non-intrusive, use some measuring devices to collect data without removing samples from the process. This can be achieved by placing analytical instruments directly into the process stream.

PAT platforms are potential candidates for real-time monitoring of CQAs in powdered and granules products. The key elements common to many powder-based manufacturing plants such as pharmaceutical industries based on a PAT framework include: (1) downstream process applications such as blending and mixing, granulation, milling and coating; (2) real-time/in-line tools such as spectroscopic methods, imaging methods, sensors and fibre optics; and (3) Multivariate Statistical Methods (MSMs) for dimensionality reduction, and multivariate regression. For instance, several unit operations of a typical tablet manufacturing process in pharmaceutical industries can benefit from PAT (see Fig. 3). In this particular case, various process variables including humidity, mixer speed and flowrate must be monitored to control CQAs such as flowability, homogeneity, and Active Pharmaceutical Ingredient (API) level in a blending process. Moreover, monitoring variables such as impeller speed is vital to control particle size in granulation and milling processes. In addition, variables like fill depth, nozzle pressure and air temperature can be closely monitored to achieve the desired tablet hardness and coating thickness.

2.2. Tools, modelling approaches and CQAs used in PAT platforms

Reliable in-line/on-line sensors or spectroscopic instruments along with multivariate and multiway chemometrics could provide informative results for the real-time quality assessment of powdered and granule products. In summary, several sensors and analytical techniques used for the quality assessments of powdered/granules products are electronic nose and tongue; spectroscopy devices such as Near-Infrared (NIR) and Ultraviolet–Visible (UV–vis) analysers; process sensors such as temperature, pressure and torque meters; and other advanced techniques such as Digital and Hyperspectral Scattering Imaging (HSI), as well as particle size analysers such as Spatial Filter Velocimetry (SFV) and Focused Beam Reflectance Measurement (FBRM), (Fig. 4). Some descriptions of the functionality of these analytical techniques for product characterisation are provided elsewhere [16,30,41–43].

After real-time data collection from sensors in a PAT system, chemometric techniques can be used for data processing and interpretation (Fig. 5). That includes: (1) *descriptive models* such as Principal Component Analysis (PCA); (2) *classification models* such as Linear Discriminant Analysis (LDA), Support Vector Machine (SVM), Partial Least Squares Discriminant Analysis (PLS-DA), *k* Nearest Neighbors (*k*NN), some kind of discriminating Artificial Neural Networks (ANNs), Soft Independent Modelling of Class Analogy (SIMCA) and Unequal Class Models (UNEQ); and (3) *prediction models* such as Multiple Linear Regression (MLR), Principal Component Regression (PCR), Partial Least Squares Regression (PLSR), Support Vector Machine Regression (SVM), and Artificial Neural Networks (ANNs) [30]. Descriptive, classification and prediction models are used to assess the repeatability of the measurements and detect clear outliers; define delimiters between established classes and calculate a separate model for each established class; and predict properties or composition parameters, respectively [30]. By employing an appropriate procedure for the corresponding experimental, dimensionality reduction and multivariate regression techniques could be facilitated, together with a suitable process monitoring and control approach.

A variety of real-time monitoring schemes using in-line or on-line measurement tools along with chemometric techniques have been implemented in a number of literature studies for invasive or non-invasive quality assessment of powdered and granule products. Table 2 summarizes some of the applied single source instruments and chemometric techniques for real-time analysis of different granular material products. Due to the large number of relevant studies available, only some studies were selected and summarized in the Table 2.

There are a number of CQAs which have been monitored in PAT platforms, including powder homogeneity, flowability, particle size, density, moisture, morphology and hardness (Table 2). The importance of monitoring these CQAs in powder manufacturing processes, and summary of PAT tools suitable for measuring them are detailed bellow.

2.3. Homogeneity:

A crucial step in many manufacturing processes is blending a mixture of powders to reach to a homogeneous system, which has a significant impact on the quality of the final product [7]. In most cases, powder mixtures should be made with high content uniformity. Usually, the homogeneity of powder mixtures can be assessed by evaluating the samples taken from the mixture. The goal of powder sampling is to collect a small amount of sample from a bulk of powder materials in such a way that the sample represents the physical and chemical characteristics of the entire bulk. The traditional samplers, e.g. thief and cross-cut, are the most commonly used instruments for powder sampling [73]. Nevertheless, fast controlling of powder homogeneity using traditional sampling techniques is not possible since sample extraction and off-line/at-line analysis of samples could squander large amount of time. Therefore, fast and accurate in-line or on-line homogeneity evaluation of powder blends are getting more attention these days. NIR chemical imaging [44], in-line NIR spectroscopy [45], Laser-Induced Fluorescence (LIF) [46], In-line Raman spectroscopy [47], and Passive Acoustic Emissions (PAE) [48] have been successfully

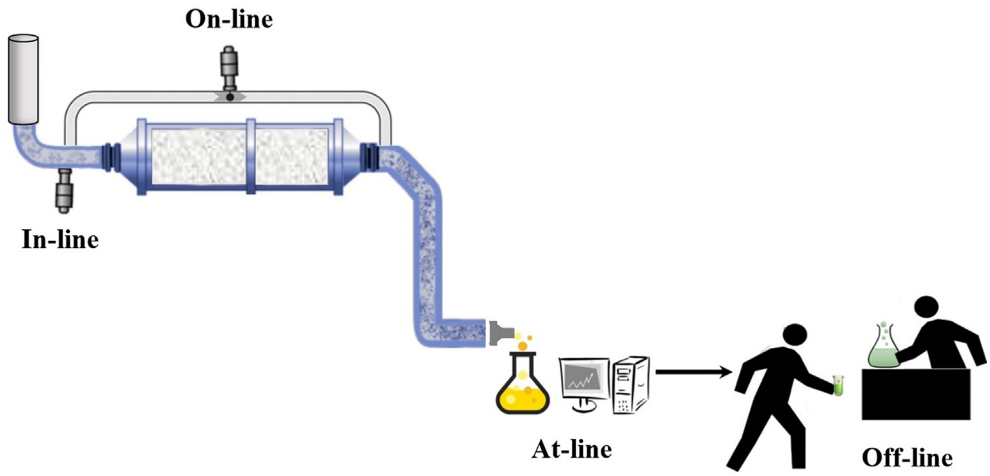

Fig. 2. Diagram of off-line, in-line, online, and at-line measuring techniques in a manufacturing process.

used instead of off-line analysis for characterising the powder homogeneity (Table 2).

NIR spectroscopy (a light absorption analytical method) uses - light in the near-infrared region (wavelengths of 700–2500 *nm*) which activates overtone and combination vibrations of molecules. Near-infrared chemical imaging uses the fusion of NIR spectroscopy and image analysis for providing the data. On the other hand, Raman spectroscopy (a light-scattering analytical method) is a technique where scattered light is used to measure the vibrational energy modes of a sample [74]. Along with a previously created calibration, the spectra resulting from either NIR or Raman spectroscopy can be used to determine the desired properties of a sample. Another spectroscopy is LIF spectroscopy which is a technique used to monitor the concentration of inherently fluorescent compounds. It functions by shining light on a sample at the analyte's optical excitation wavelength, and then collecting the light from the analyte at its emission wavelength perpendicular to the incident beam. The other technique reported for homogeneity analysis is based on acoustics which is the production by a source, transmission through a medium, and reception by a receiver of energy in the form of waves [75,76]. Another inexpensive and non-destructive device for discriminating between different product qualities is an electronic devise such as an electronic nose (E-nose) which compromises of a combination of sensors to allow the discrimination of products with different characteristics. Designed to simulate the process and mechanisms of human olfactory recognition, it can successfully be used for food flavour examination [77–82] and powdered and granule characterisation [83–87].

2.4. Flowability:

The most common problems encountered in solid processing plants occur during transporting of solids and handling of fines [88,89]. Solid powder components may not flow smoothly, and process delays are often involved due to poor flow behaviour of powder materials. For instance, many drug powders used in pharmaceutical industries have very poor flowability. This accordingly could affect manufacturing and other operations like blending and tableting, leading to problems such as the lack of content uniformity and significant loss of revenue [11]. These problems are caused by failure to incorporate accurate flowability measurements into the design. The end result is frequent stoppage of the process, involving costly loss of production time and inefficient use of staff to restore the flow. The followability of powders could be affected because of variations in powder properties e.g. size, humidity or undergoing load e.g. shear stress/compaction on bulk of powders. Many types of testing equipment exist to measure the flowability of bulk solids off-line or at-line. Shear Cells [90], Sevilla Powder Tester [91] and the Freeman FT4 Powder Rheometer [92] are the most established methods of powder flow measurement. However, in-line or on-line measurements of powder flow is challenging and demand further investigations. A number of research successfully implemented NIR Spectroscopy [57], Non-invasive Acoustic Sensors [58], Revolution Powder Analyzer (RPA) [56] and Capacitance-based approach [59,60] instead of off-line analysis for the characterisation of powder flowability (Table 2).

The RPA consists of a rotating drum covered on both sides with transparent glass, where a camera is positioned in a way to record pictures of the rotating drum. Flowability can be measured by recording black-and-white pictures of the powder and the avalanches within the drum [56]. Capacitance-based approach can also be used for flowability measurement, which is a non-invasive sensing technology with fast data acquisition to generate a whole volumetric image of the region enclosed by the capacitance sensors from the measured capacitance [93].

2.5. Particle size

Real-time monitoring of Particle Size Distribution (PSD) is also important in continuous processes as it highly affects downstream process efficiency [94,95] and final product quality [96,97]. Extraction of information of granules properties such as PSD is tempting, as it could enhance the process knowledge without the need for new capital investments. For instance, monitoring and control of PSD is very important aspect in continuous granulation and drying process in pharmaceutical products. Formation of too many fines can cause some part of materials to stick to the tablet press, resulting in non-uniform drug content due to segregation, while altering the tablet disintegration and dissolution profiles. On the other hand, too many oversized particles can change the granules drying profiles [54]. Among traditional off-line techniques of PSD characterisation are Sieving, Laser Diffraction [98] and Microscopy [99] which are all time-consuming. However, in-line or on-line particle size analysers could offer fast, and non-destructive PSD measurements, enabling the opportunity of real-time feedback or feedforward process control, and optimal process operation which are critical to the migration from batch to continuous manufacture [52].

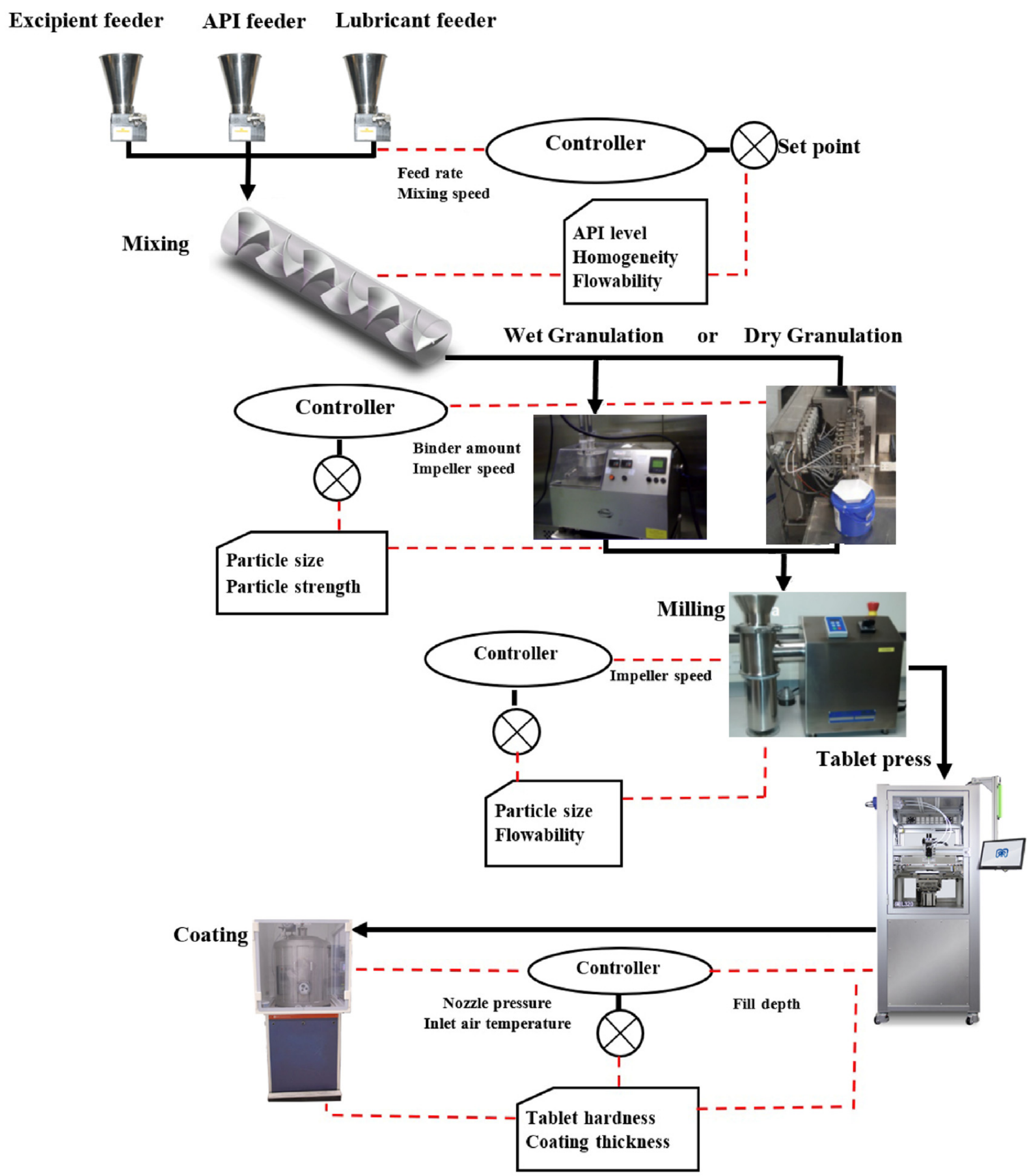

Fig. 3. Unit operations in a typical pharmaceutical industry for tablet production (Images licenses:Tablet press: "German RepRap 3D-Drucker L320" by Liebimprinzip is licensed under Creative Commons Attribution-Share Alike 4.0 International license.Coating: "Varian 3119 coating deposition machine" by Guillaume Paumier is licensed under Creative Commons Attribution-Share Alike 3.0 Unported license. Mixer: "Static mixer" by Christian Lindecke is licensed under Creative Commons Attribution-Share Alike 3.0 Unported license.), [38–40].

Audible Acoustic Emissions (AAEs) [50], SFV Probe [51], Particle Vision Microscope (PVM) [52], Torque [53], and NIR spectroscopy [54,55] have been successfully used instead of off-line analysis for the characterisation of particle size in powders (Table 2). SFV probe is a PAT tool that can be installed in a process to determine in-line particle size and PSD by measuring the rate and chord length of the particles [100]. PVM can also be used as an in-line imaging method for capturing a 2-D projection of particles to determine the particle size [52]. In addition, process parameters affecting CQAs such as torque can be successfully used as an in-process measurement and control of granule size during a granulation process [53]. The torque is a process variable which is representative of the power required to mix and/or transport the material and rotate screws/paddles [101].

2.6. Density

Monitoring the bulk density of either static or moving powders particularly inside a process line is essential for manufacturing high-quality products. In particular, granular materials are two-phase systems including gas as a continuous phase and a dispersed phase containing solids of various sizes. Therefore, the behaviour of powder materials depends not only on the properties of individual particles, but also the properties of the assemblies of particles and the interactions between these assemblies and the continuous phase [102]. The bulk density and tapped density can be determined using graduated cylinder off-line, by measuring granule weight and volume, before and after employing an automatic tapper [16]. However, measuring the variabilities in properties of particle assemblies in real-time and setting up corrective actions

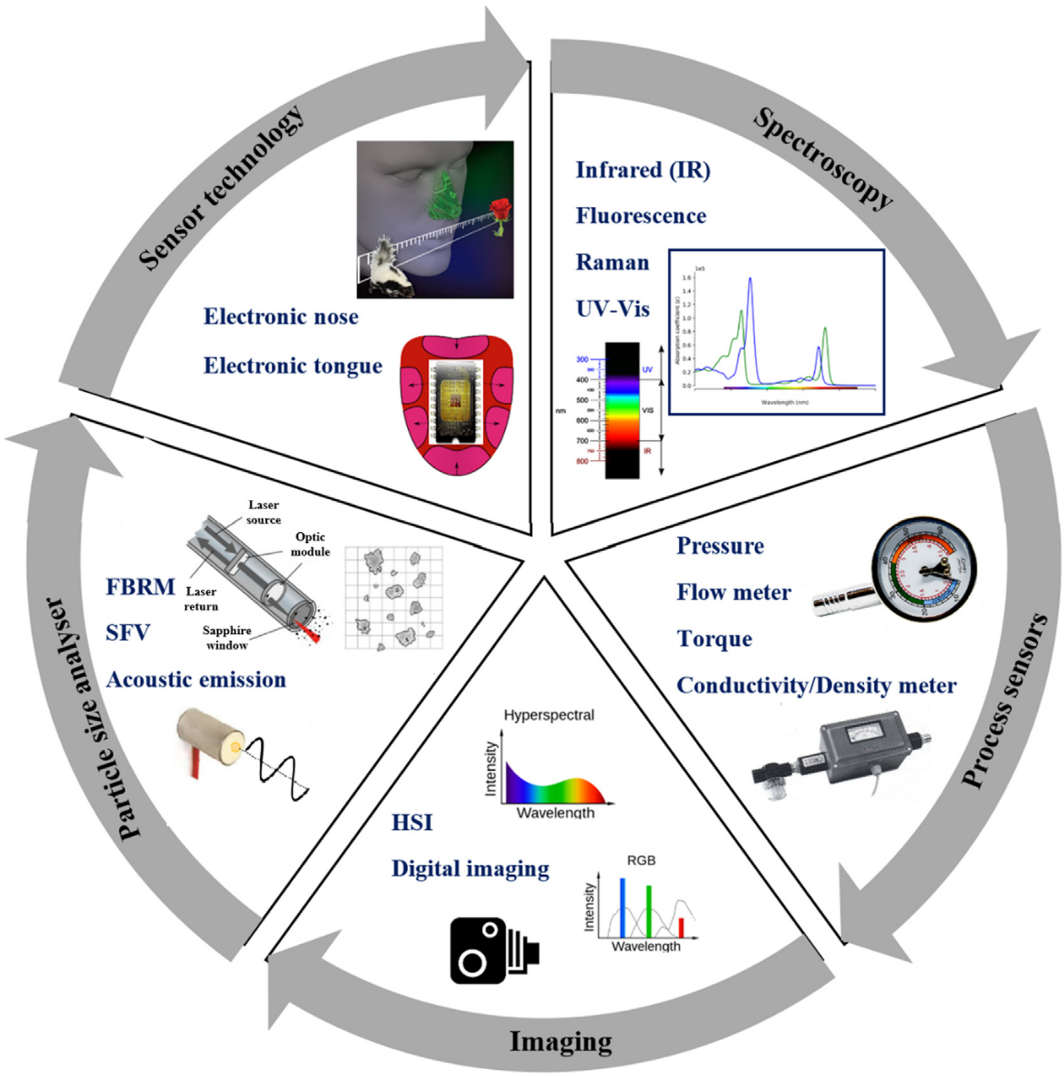

Fig. 4. Sensors and analytical techniques used for the quality assessments of powdered and granule products (Images licenses:"An Electronic Nose Estimates Odor Pleasantness" by Genia Brodsky and Noam Sobel is licensed under Creative Commons Attribution 2.5 Generic license."Taste buds" by MesserWoland is licensed under Creative Commons Attribution-Share Alike 3.0 Unported license."Spectral sampling RGB multispectral hyperspectral imaging" by Lucasbosch is licensed under Creative Commons Attribution-Share Alike 4.0 International."Chlorophyll Absorption Spectrum" by Serge Helfrich is licensed under Creative Commons Attribution-Share Alike 4.0 International license."Light spectrum (precise colors)" by Fulvio314 is licensed under Creative Commons Attribution-Share Alike 4.0 International license."LVDT flow meter" by Hms1840london is licensed under Creative Commons Attribution-Share Alike 4.0 International license."Pressure gauge" by Twitch Chess Streamer is licensed under Creative Commons 2.0 license.).

before they can influence the product quality are challenging [17]. This is specifically important in the manufacturing of pharmaceutical solid dosage forms. Powder density variation could produce variabilities in tablet mass, dissolution rate and hardness during tablet manufacturing processes. Incorrect amount of drug could be delivered to patients due to variations in tablet mass, leading to further health problems [62]. Therefore, it is really important to monitor and control the relative densities of the intermediate and final products which are highly critical for the product quality and consistent product performance. Acoustic Emissions [50], Terahertz In-line Sensing [61] and Real-time NIR Sensor [17,62] were used for characterising the bulk density as shown in Table 2. Terahertz Time Domain Spectroscopy (THz-TDS) is a promising analytical tool for measuring the pore structure of tablets [103]. The terahertz spectral region covers the range from 0.1 to 4 THz (3 mm to 75 μm in wavelengths) [104]. The advantage of THz-TDS compared with NIR, Mid-Infrared (Mid-IR) and Raman spectroscopy is that it operates at a much longer wavelength, hence it is inherently less vulnerable to the scattering effects in powders [103].

2.7. Moisture content

Product quality, chemical stability, shelf life, and reactivity of many granular materials such as pharmaceutical products can be affected by water [105–107]. The quantification of the water content in drug products is important for demonstrating compliance with the quality standards. Moisture content in powders is a CQA as it could adversely affect many manufacturing unit operations including conveyance, compaction, granulation, drying, etc. if not monitored properly [108–110]. Moreover, in the case of excessive moisture during manufacturing processes such as fluidization beds, many particles can agglomerate impacting the stability of the process [13]. There are many time-consuming techniques for the determination of water content in granular materials such as Karl Fischer Titration for pharmaceutical products [111]. However,

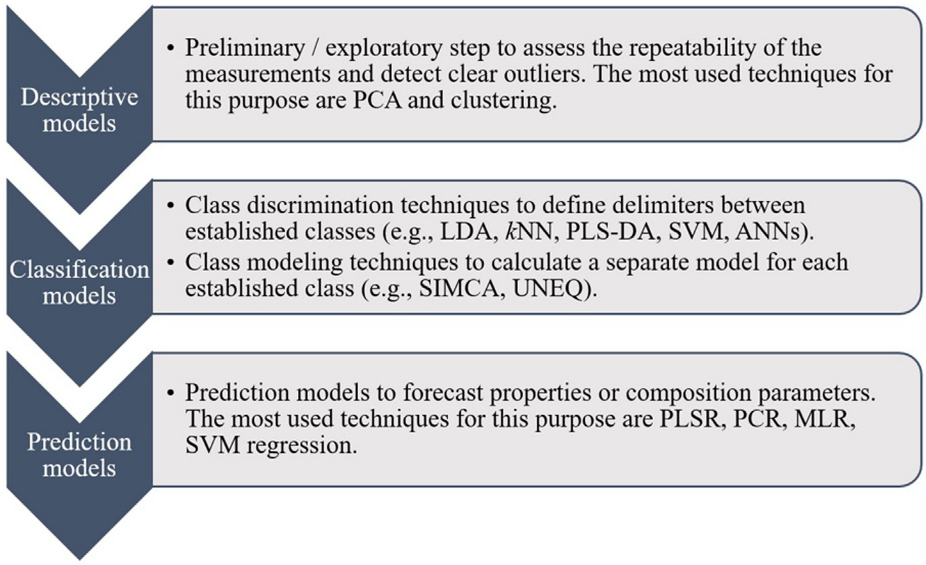

Fig. 5. Chemometric techniques used for the analysis of data from instrumental apparatus.

it would be favourable in the development of manufacturing processes to implement accurate in-line or online techniques to facilitate determinations of moisture content as early as possible.

Instead of off-line analysis, In-line NIR Spectroscopy [64,65], NIR Chemical Imaging [67], Microwave Sensor [66], and a Capacitive Sensor [68] can be used for the characterisation of powder moisture level (Table 2). The most common dielectric transducer used for powder characterisation is Capacitive Sensor which is a rapid and non-contact method, where parallel conductive plates are attached to the outer layer of a measuring vessel. It enables creating what is essentially a capacitor, the capacitance of which is related to the permittivities and quantities of dielectric materials [112,113]. Most materials' dielectric properties depend on factors including the chemical composition, structure of the material, and permanent dipole moments associated with water and any other molecules making up the material. On the other hand, the microwave sensors were developed to set up better methods for the measurement of the permittivity and to investigate the relation between the permittivity and the physical properties of materials [114]. An electromagnetic wave in a microwave sensor has a wavelength in the approximate range from 1 *mm* to 1 *m* (the region between infrared and short-wave radio wavelengths) [115].

2.8. Hardness

One of the most investigated properties of granular materials is hardness which depends on the elemental structure and chemistry of materials. Standardised tests, such as Uniaxial Compressive Strength [116], Rockwell, or Vickers and Schmidt Hammer Test [117] or Scratch Hardness Tester [118] are normally used to measure the mechanical properties of particles such as rocks. However, there are instances when it is not feasible to perform the standardised tests, due to time- and cost-consuming nature of sample preparation or because it is not applicable to collect a significant enough set of results. Therefore, determination of granular material hardness, such as quantification of tablet hardness [20] or rock hardness [116], and granule compressibility and strength [19], using rapid in-line or on-line techniques would be useful. As can be seen in Table 2, on-line spectral measurements using NIR Process Analyser [18,19] and Process Variables [69] could be implemented for the characterisation of hardness. Further studies have shown the applicability of a real-time NIR Spectroscopy for monitoring different CQAs including powder homogeneity, moisture, bulk density, tensile strength, Young's Modulus, median size and Hauser ratio [71,72].

It should be mentioned that lack of reliability and limitations of some instruments are the main issues of applying a single source instrument in a continuous manufacturing of powder-based products [119]. For instance, Fig. 6 illustrates the main variables that could have an adverse impact on the collected data based on applying a single spectroscopy device in the process (classed as process, equipment and material). The powder process variables are highly interactive, impacting the overall closed-loop control system performance [120]. For instance, interference of some process parameters such as humidity and temperature [121] on the spectral data could lead to the reduction of accuracy in extracting the desired information from a spectroscopy sensor. Second source of issue may arise due to failure of the equipment. Sometimes one sensor may be in fault, data acquisition system may fail, some sensors may produce very low sampling frequency, sensor touching windows may be blocked/contaminated by powder dust during continuous process, or one sensor has to be removed from the process due to maintenance or replacement. All of these factors could adversely impact the continuous process monitoring and control, resulting in lowering the product quality, increased production costs, or even dangerous situations for plant personnel or environment [122]. The last factor impacting the collected data of an instrument is the nature of materials used in the manufacturing process. In many industries, the end product composition is complex and may contain compounds with functional groups having nonselective spectral bands. Sometimes, a powder mixture up to 10 to 20 ingredients would be necessary to meet the acceptable quality standard of a final product [7]. The lack of spectral band selectivity for some compounds in a powder mixture [123] could be the main disadvantage when using a single spectroscopic tool for the analysis of quality attributes. Therefore, big data management of multi-sensors could be an alternative option for improving the model prediction efficiency in a continuous process of powdered and granule materials which is described in section 3.

Table 2
Single source instruments used for the characterisation of powder properties.

Objective	Process	Materials	Real-time instrument	Chemometric	Ref.
Powder uniformity	Continuous twin screw granulation	Pharmaceutical powder blend	NIR Chemical Imaging	PCA and PLS and CV	[44]
	Chute	Pharmaceutical powder blend	An in-line NIR spectroscopy	PLS	[45]
	Blending process	Pharmaceutical formulation	LIF	LIF profile	[46]
	High speed electrospinning and milled	Pharmaceutics	In-line and at-line NIR and Raman spectroscopy	PLS	[47]
	V-blender	Glass beads	PAE	The emission amplitudes profile	[48]
	HTPB propellant slurry	Hydroxyl-Terminated Polybutadiene (HTPB) propellants	NIR-based methodology	OPLS-DA	[49]
	High-shear wet granulation	Pharmaceutics	AAEs	PLS and OPLS	[50]
	Fluidized bed	Placebo mixture	SFV probe	Regression	[51]
	Glass jacketed tank reactor	Polystyrene (PS) particles	PVM	PLS	[52]
	Twin-screw wet granulation	Pharmaceutics	Torque	MLR	[53]
Particle size	Granulation and drying process	Pharmaceutics	NIR spectroscopy	PLS	[54]
	Powder storage	Milk formula	NIR spectrometers in diffuse reflection mode	PLS	[55]
Flowability	Additive manufacturing	Fe- and Ni-based powders	RPA	Regression	[56]
	A twin screw loss-in-weight feeder	Pharmaceutics	Transmission NIR Spectroscopy	PLS	[57]
	Pneumatic transport	Glass beads and PVC	Non-invasive acoustic sensors	Acoustic raw signal	[58]
	Food processing	Beverage powders and their mixtures	Capacitance-based approach	The dielectric differences profiles	[59]
	Tablet Manufacturing Process	Pharmaceutics	Capacitance-based sensor	Mass flow rate profiles	[60]
Bulk density	High-shear wet granulation	Pharmaceutics	AAEs	PLS and OPLS	[50]
	Moving powder bed	Pharmaceutics	Terahertz in-line sensing	Linear models	[61]
	Powder blending process	Pharmaceutics	Real-time NIR sensor	PLS model	[17,62]
Moisture content	Fluidized bed dryers	Corn particles	Electrostatic sensor array	Linear model	[63]
	Drying process	Tapioca starch	In-line NIR spectroscopy	PLS	[64]
	T win-screw wet granulation, vibrational fluid-bed drying and milling	Pharmaceutics	NIR spectroscopy	PLS	[65]
	Dairy processing industry	Milk powder	Microwave sensor	Linear least squares method	[66]
	Fluid bed drying	Pharmaceutical granules	NIR chemical imaging	PLS and Elastic Net Regression (ENR)	[67]
	Spray dried process	Gelatin powders	A capacitive sensor	Dielectric properties profiles	[68]
Hardness	Roller compaction	Pharmaceutical powder blend	On-line NIR Process analyser	PLS	[18,19]
	High shear wet granulations	Drug samples	Granulation process variables such as impeller speed	Combined experimental design and PCA	[69]
Morphology	Crystallization	An organic compound	Non-invasive on-line imaging technique	Real-time image analysis	[21]
	Milk powder plants	Milk powder samples	Light microscopy combined with image processing algorithms	Real-time image analysis	[70]
Multi-properties	High-shear wet granulation process	Pharmaceutical powder blend	NIR spectroscopy	PLS	[71]
Multi-properties	Roller Compaction	Pharmaceutics	Real-Time NIR Monitoring	PLS	[72]

3. Multi-sensors data fusion for managing big analytical data

3.1. Data fusion approaches

Data processing techniques based on data fusion methods can be potentially used for effectively analysing the big-analytical-data. Data fusion is a data-driven approach by which complementary data displaying significant variations could be merged with the desire of increasing the model performance and robustness. The main advantages of employing data fusion techniques for analysing the collected big data in PAT system are summarised below:

o Converting large amount of complex datasets obtained from multiple sources to a holistic, accurate and useful model for monitoring and control of process. Superior capabilities of multi-sensors data fusion include simultaneous multivariable measurement, reduction of complexity of big data streams and achievement of more accurate output compared to an individual source, while ensuring robust monitoring of a continuous powder process.

o Providing possibilities for obtaining robust predictive models form merging the data obtained from multiple available sensors in the process rather than employing expensive and/or hard to install analysers for measuring the CQAs. It provides the possibilities for developing soft-sensors (virtual sensors) from available process sensors which can then be used as a backup sensor when a critical hardware sensor is in fault or removed.

Using data fusion approaches, integration of the data collected from several analytical techniques can be performed using different strategies based on low-, mid- and high-levels. Fig. 7 shows a schematic representation of different data fusion techniques. The number of input sources could vary depending on the scale of the process. Basically, two, three or even up to five sources can be merged together [124–128].

A common methodology proposed by Steinmetz et al. [129] can then be used to access the quality of the model based on data fusion approach (Fig. 8).

Different data fusion approaches for the interpretation of big datasets are summarized below:

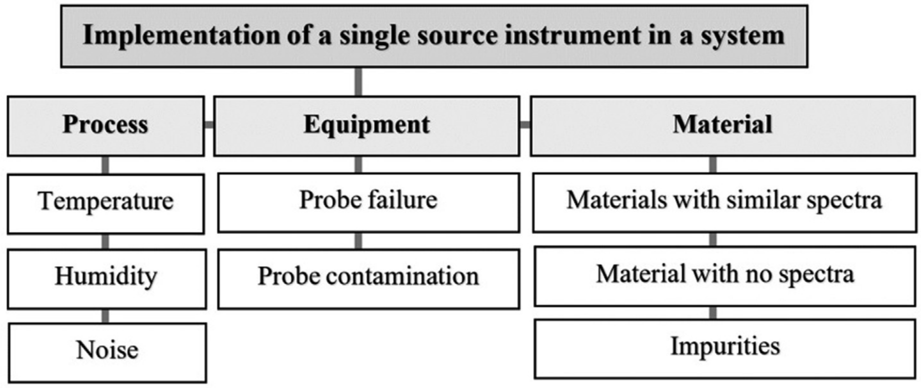

Fig. 6. Variables impacting the collected data of a single spectroscopy instrument used for the evaluation of CQAs in a continuous powder process.

3.2. Low-level data fusion

Data from all sources can simply concatenated into a single matrix (rows as samples and columns as variables), and then the new matrix will be used for calculating a single model using classification or prediction models. This method is called a low-level fusion which is very simple. In doing a low-level data fusion, the analyst must decide which variables are expected to be more relevant to the problem. This process is called variable selection by which uninformative variables with excessive noise or the ones non-correlated to the property of interest can be discarded before further analysis. Stepwise Selection (e.g. Forward Stepwise or Backward Stepwise) [130], is one method of variable selection where variables are chosen to enter or leave the model following a selected criterion. On the other hand, regions of variables can be selected instead of single variables when data are highly correlated. For instance, performing Forward/Reverse Variable Selection of Variable Intervals can be done by Interval PLS (iPLS) [131]. Genetic Algorithms (GAs) [132], Analysis of Variance (ANOVA) variable selection [133], Clustering around Latent Variables (CLV) [134], and Variable Importance in Projection (VIP) [124] are among other variable selection methods.

3.3. Mid-level data fusion

High data volume and predominance of one data source over other sources are among the disadvantages of low-level data fusion. The disadvantages of low-level fusion could be overcome by applying a mid-level fusion strategy, by which the extraction of relevant features from each data source separately, and then concatenating them into a new matrix before using classification and regression analysis are performed for minimizing the number of variables. Data dimensionality can significantly be reduced by feature extraction while filtering block noises. For instance, score from PCA or PLS-DA [124] can be used to produce the latent variables from the signals of each instrument. Other techniques for feature extraction are Multivariate Curve Resolution [135], Kernel Based Methods [136], Independent Component Analysis [137], Wavelet Transform [138], LDA [139], Multiblock Methods such as Hierarchical PCA/ PLS [140,141] and Multiblock PCA/PLS [142] or Serial-PLS [141].

3.4. High-level data fusion

Testing all the combinations of feature extraction methods and pre-processing methods in Mid-level data fusion is sometime cumbersome and computationally intensive. Therefore, the use of high-level data fusion might be useful for some cases. In a high-level fusion, separate classification of regression models are first developed for each data source. Then, the combination of the results from the individual models will produce the final identity declaration [30]. In high-level fusion, the classification or regression model that works best for each block must be determined. In this case, their combination could perform better than individual models. Therefore, results from inefficient techniques do not worsen the overall performance since every individual matrix is treated independently. Accurate data pre-processing and considering the correlation of the responses between sources are the important prerequisites for high-level data fusion.

3.5. Main considerations before performing data fusion

Overall, the main considerations for integrating data for developing robust data-driven models are discussed below [25–28]:

3.5.1. Understanding the structure of data generated by analytical devices

Focusing on the structure of the data acquired by different types of analytical instruments, experimental setups, and other types of sources is important. Due to heterogeneous nature of samples, specific properties can be detected by each individual instrument. Thus, understanding how datasets can be fused to extract the combined relevant information and not distort results due to an incorrect fusing method is really critical. Prior to selecting the data fusion approach, exploring the instrument with which data is acquired is important (Fig. 9). Zero-order instruments also called one-way data, can produce a single response per sample such as temperature, or concentration of a compound; First-order instruments also called two-way data, can enable measuring the properties of a sample for different dependent variables including data acquired from analytical techniques such as spectroscopic; and second-order also called three-way data, can provide a full matrix for each sample (the two directions of the matrix are dependent variables) [25]. Also, understanding other concepts such as mode and multivariate is important in defining the structure of data. For instance, when data is acquired by two different spectroscopic techniques such as UV–vis and NIR spectroscopy instruments, spectral profiles are multivariate as the responses are acquired at several wavenumbers. Also they are multimodal as the two different spectroscopic techniques represent the modes.

3.5.2. Optimising the pre-processing of the collected datasets

Considering the best data pre-processing technique is a critical part of data analysis task to extract the most useful information from data. This can be achieved by finding suitable strategies to remove undesirable effects such as artefacts (e.g. baseline and peak

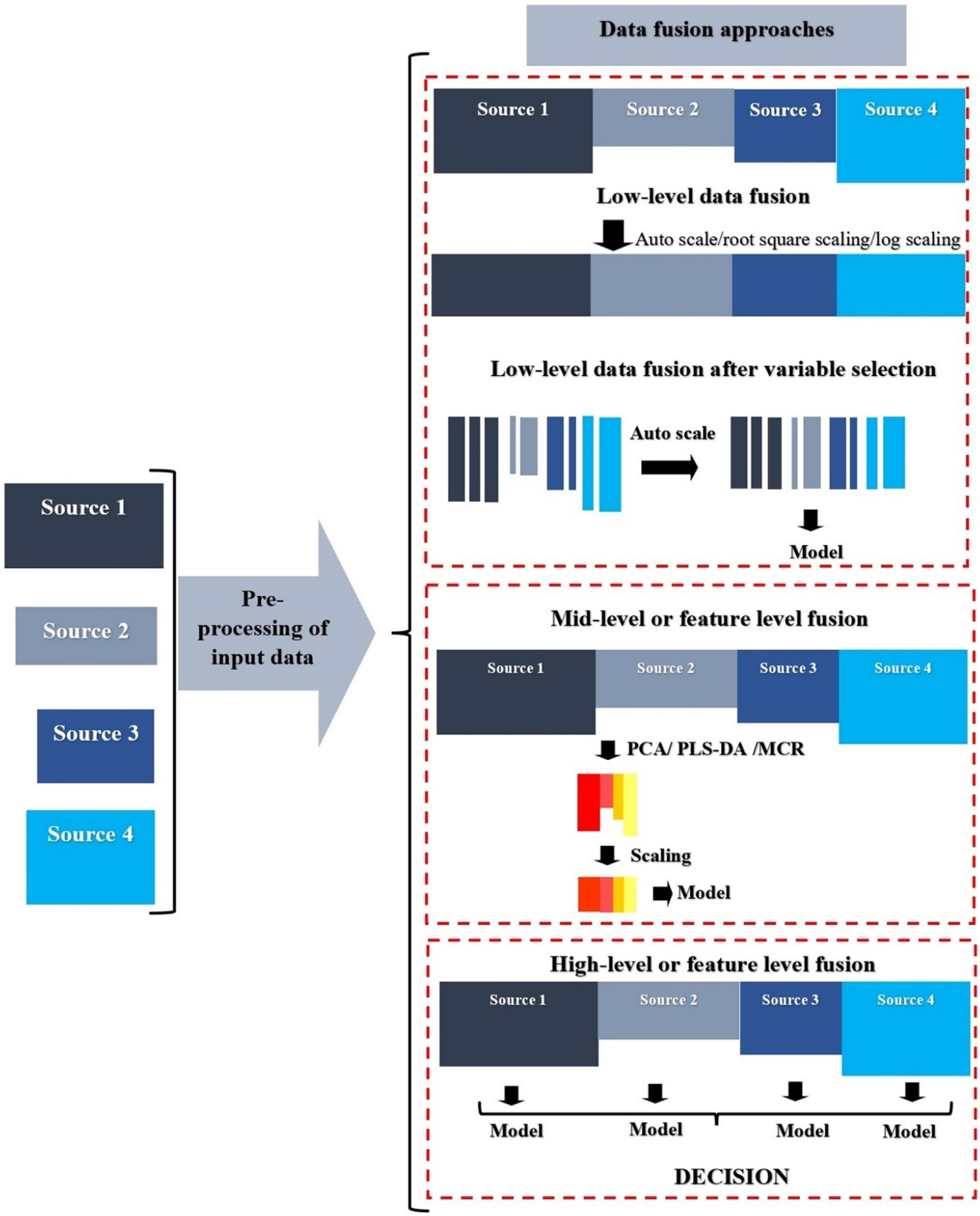

Fig. 7. Different data fusion approaches (low-level, mid-level and high-level).

shifts, noise, systematic factors, missing data, multiplicative effects, etc.) [27,28], Fig. 10. This step is really crucial to maximize the potential of improving the quality of information extracted from data. Each artefact comes from its own background causes. For instance in the case of spectroscopy, it can be observed due to a human error during measurements, and/or the complex interaction of light with the physical structure of the sample.

Overall, pre-processing steps start from the intra-block level, proceeding to the inter-block levels [27] as follows, which are important particularly for a low-level data fusion:

Level I: intra-block Signal-to-Noise Ratio (SNR) improvement and feature enhancing;

Level II: intra-block scaling for equalizing the importance of the intra-block predictive components;

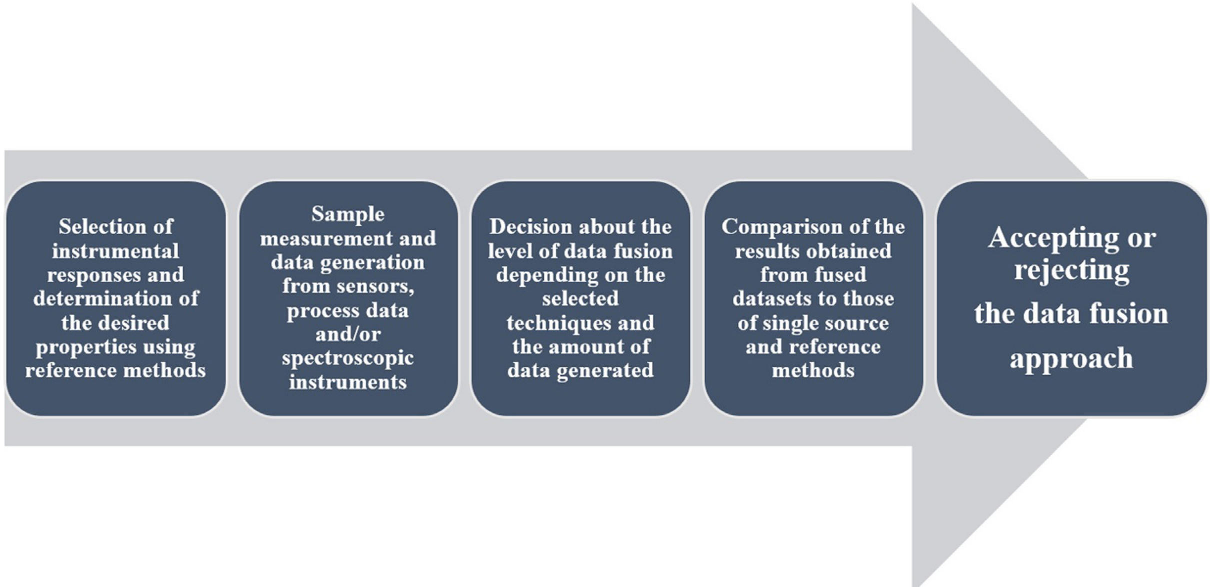

Fig. 8. A common methodology to access the quality of the products using data fusion approaches.

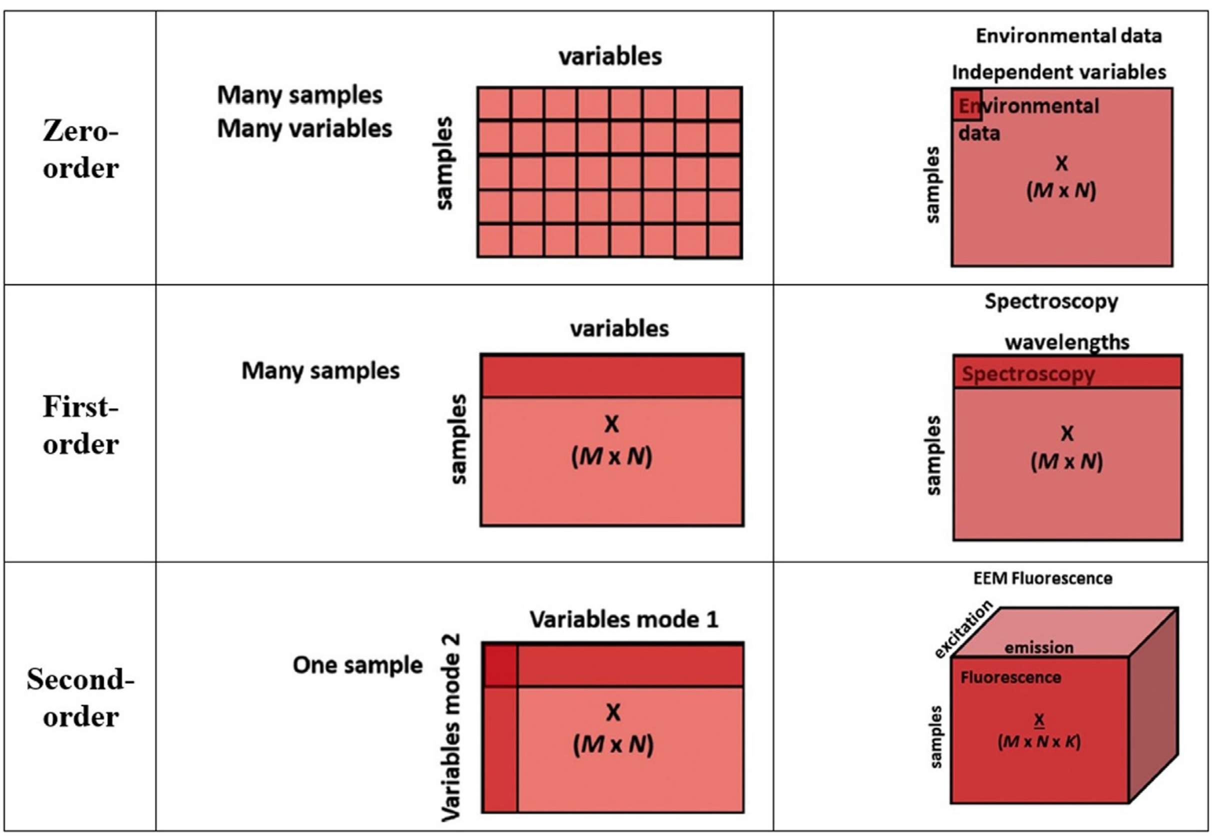

Fig. 9. The structure of the data acquired by different tools (M samples, N and K variables), reprinted from Azcarate et al. [25] with permission from Elsevier.

Level III: balancing inter-block effects and making their contributions commensurate in the analysis.

Obtaining the appropriate pre-processing method is usually not a straightforward task as it depends on the structure of data, the purpose of the analysis, and the modelling method selected. In most cases, the selection of pre-processing strategy involves extensive trial and error processes, or is achieved by the user experience on similar cases. The overviews of the correction of all the types of artefacts for noise removal, missing data imputation, multiplicative effect correction, baseline correction, and peak alignment were presented elsewhere [27,28].

Overall, some pre-processing techniques before implementing low-, mid- and high-level data fusion strategies are Standard Normal Variate (SNV) for Mid-Infrared (MIR) [124], Multiplicative

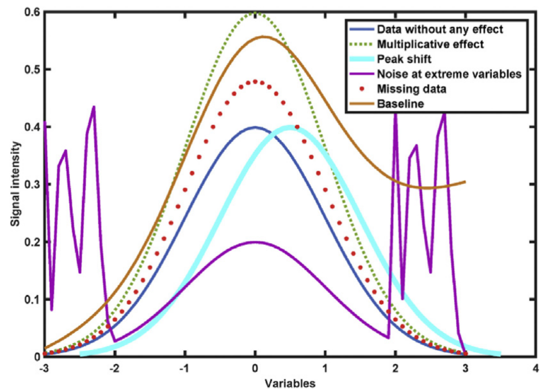

Fig. 10. Example of several artefacts for visible and NIR data, reprinted from Mishra et al. [28] with permission from Elsevier.

Scatter Correction (MSC) for NIR and MIR spectra [143], baseline corrections and derivatives for eliminating baseline shifts in infrared spectra and UV–vis spectra [144], and scaling/normalization for Mass Spectra (MS) [145]. In order to compensate for different measuring scales and variability of datasets in low-level fusion, additional pre-processing such as autoscaling, root square scaling and log scaling may also be required [146]. This could prevent one block from being dominant. Finally, data is mean-centered before building the model after data are merged.

3.5.3. Selecting an appropriate data fusion method

One of the great challenges of multi-sensory data collection in a continues process monitoring and control loop is how to meaningfully combine not only different variables of an individual sensor outputs but also blocks of sensors to achieve the best and quick process automation system [147]. Implementing an appropriate data fusion method can be a laborious task and should be selected wisely. Table 3 summarizes the comparison of different data fusion strategies which shows that factors including the order, scale and structure of data, the level of noise and redundant information of original data, dataset variability, model development and precision could all impact the final decision for implementing a suitable data fusion approach. Therefore, selection and implementation of an appropriate big data analysis strategy according to the type of process and the producing datasets would be essential to integrate all the collected data.

3.6. Current status of data fusion used for powdered and granule characterisation

Data fusion strategies have been successfully used for the performance improvement of PAT platforms. For instance, instruments including vibrational spectroscopy (NIR and Raman spectroscopy), and colour quantification (colorimetry and image analysis) were used for the quantification of the API in an electrospinning case study [148]. A Mid-level data fusion approach (data compression through latent variables and ANN for regression purpose) was reported as an efficient method to quantify the API. Fusion of Fourier Transform Infrared (FTIR) spectroscopy and Powder X-ray Diffraction (PXRD) was employed by Haware et al. [149] to improve the accuracy of quantifying API concentration in a mixture of pharmaceutical powders. The efficiency of Fusion of Preprocessed Data (FPD) and Fusion of Principal Component Scores (FPCS) were compared. PLS model developed based on FPD did not improve the prediction error, while a PLS model built on FPCS yielded a better accuracy prediction than PLS models based on individual FTIR and PXRD datasets which could be attributed to the noise removal and data reduction associated with using PCA as a pre-processing tool. Raman spectroscopy, image analysis and combined Raman and image analysis were compared against each other by Sekulovic et al. [150] to characterize the solid form composition of a particulate raw material. It was found that integration of image analysis and Raman spectroscopy datasets using PLSDA classification models had the potential for accurate detection of low amounts of unwanted solid forms in particulate raw material samples.

In another study, Tahir et al. [151] utilized a real-time process monitoring and fault detection scheme for a pharmaceutical hot-melt extrusion process. Hybrid soft sensor and Raman-based PLS

Table 3
Comparison of data fusion strategies.

	Low-Level	Mid-Level	High-Level
Method description	Also called data augmentation or multi-block analysis, it aims at coupling of datasets in the samples or the direction of the variables, by directly placing the datasets next to the other or coupling them across the variables.	A two-step methodology: First, extracting relevant features from each data source separately; and second, concatenating these outputs to build a single matrix to be processed.	Is a suitable strategy to integrate data by treating each data block independently and, then fusing the outcomes (predictions) to analyse them as a single block.
Benefits	-The most straightforward and simple way of data fusion. -Used as a first approach when there is more than one dataset available. -Easily applied in data concatenation of zero- and/or first-order. -Not having the difficult problem of needing an optimal extraction of features. - Efficient for the fusion of data with a similar structure.	-It solves the issue of concatenating data blocks of different orders. -Preferred when first-order data to be combined with a zero-order. -Leading to a better final data fusion model as cross-validation is made in each model. -Frequently used for handling spectroscopic data as a huge amount of information is involved.	-It solves the issue of concatenating data blocks of different orders. -Encompasses simple development since only the outputs coming from different models are fused. -Does not need to adjust an adequate scaling since each model being fitted independently with its best scaling.
Challenges	-Complex to be used for second-order data. -Needing optimisation of prior and post data pre-processing to tackle the noisy and redundant information. -The data block scaling is more critical in this level with respect to other fusion approaches.	-Performing exhausting methodologies for data fusion due to needing the optimisation of feature selection algorithms. - If a proper data reduction is not performed, useful information can be left out in the residuals.	-Less used in the literature due to major complexity compared with other data fusion approaches. -The order of combining the predictions obtained affects the final decisions.

calibration model were utilized for the prediction of Paracetamol concentration. Detection of process faults and raising alarms were successfully implemented using the prediction models, along with PCA and Statistical Process Control (SPC). The results of Tahir et al. [151] showed that a PLS calibration model to predict API concentration based on only in-line Raman spectra on its own was not sufficient to detect the related faults in the process. Therefore, they integrated a back-up soft sensor [42,122] with PLS calibration model obtained from Raman spectra to predict the API concentration. Predictions based on the two independent sources, along with process data, were then fed into the developed PCA and SPC monitors (Fig. 11). Implementation of two-sensor approach facilitated the early detection of common process faults which could otherwise remained undetected by applying single-sensor monitoring scheme.

Table 4 summarises further available research on the application of data fusion for powder and granule characterisation. As can be observed in Table 4, a wide range of studies was done on soil characterisation for the determination and classification of both physical and chemical properties owing to a wide range of soil sensors that are available in market. However for other powder sectors, only a few research has been conducted which investigated only the chemical properties of the powder samples (e.g. composition of pharmaceuticals, coffee, milk and flour powder mixtures). Therefore for other powder sectors such as food, cosmetic, paint, metal, agriculture, etc., further studies and opportunities could be provided to investigate the performance of data fusion for measuring the CQAs, including the physical properties such as density, porosity, surface texture which could significantly influence the flowability and handling properties of powders. Several future perspectives for the application of multi-sensors data fusion in powder and granule characterisation based on authors' view are described in section 4.

4. Future perspectives of data fusion for powdered and granule characterisation

The research area of closed-loop controlling systems by means of multi-sensors data fusion is in its infancy, and is an open area of research for academics and technology providers. Implementation of multi-sensors data fusion could potentially avoid delays in the process monitoring and control. With respect to this, following opportunities may be brought in the field of PAT for the assessment of physicochemical attributes of powders and granule materials.

4.1. Multi-sensors data fusion for the prediction of CQAs

By applying multi-spectroscopic data fusion, homogeneity evaluation of a wider range of powders could be possible (Fig. 12). The accuracy of concentration estimation could be increased for compounds with similar or nonselective spectral bands, but different in other properties such as fluorescent or MIR bands. For instance, greater than 60 % of pharmaceutical powders have a degree of fluorescence property that particularly could be detected by LIF spectroscopy only [172]. Several advantages of LIF over absorption spectroscopy such as NIR spectroscopy are: (i) excellent detection sensitivity because a signal is observed against a dark background; and (ii) making it possible to obtain two and three dimensional images as the emitted radiation can be collected at various angles with respect to the collimated laser beam [173]. Therefore, the results of LIF can be complementary to those obtained from other spectroscopic systems such as NIR. Multi-block methods [26] could potentially be applied to fuse the spectral data, after applying the optimum pre-processing techniques on each spectral range [27].

Non-spectroscopic profiles could also be integrated to spectroscopic data to interpret the powder's homogeneity (Fig. 12). For instance, on-line electrical capacitance could be installed in the system for measuring the dielectric permittivity of powder mixtures. This technique has been previously investigated by Ehrhardt et al. [174] to examine the segregation pattern of discharging silicon carbide and sugar mixture in funnels, and a drum mixer. However, it should be stated that electrical capacitance sensors can only be applicable to those materials with noticeable variations in dielectric properties. Potentially, the use of feature selection methods based on mid-level data fusion could be considered in this case, as a huge amount of information is involved in the spectroscopic data compared with electrical capacitance tools. In fact, mid-level data fusion is preferred when first-order data should be combined with a zero-order or another first-order dataset to successfully exclude the uncorrelated variables associated with spectral data (Table 3).

Physical attributes of powders could also be qualitatively and quantitatively estimated by vibrational spectroscopy and chemometrics approaches [175]. Table 2 clearly shows that vibrational spectroscopy such as NIR has been successfully used to determine several physical attributes of powder and/or granule products including particle size, bulk density, flowability and hardness. However, the measurement accuracy of NIR may not be sufficiently enough to evaluate the physical characteristics of some powder types on its own. For instance, Wang et al. [176] investigated the

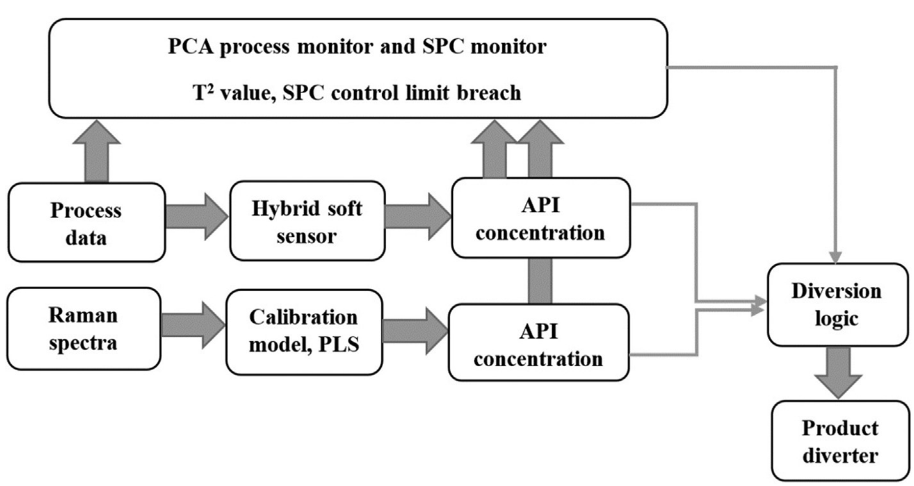

Fig. 11. Process monitoring scheme in PAT, [151].

Table 4
Data fusion for powder and granule characterisation in solid samples.

Type of powder/granular matter	CQAs	Fused sensors	Data fusion approaches	Reference
Pharmaceutical powder	APIs authenticity investigation	HPLC, NIR spectroscopy, Proton Nuclear Magnetic Resonance spectroscopy and XRD	Low-level or mid-level	[152]
Pharmaceutical powder	Quantification of active pharmaceutical ingredient	NIR spectroscopy, Raman spectroscopy, Colorimetry and Image analysis	Mid-level data fusion	[148]
Pharmaceutical powder	Quantification of active ingredients	FTIR and PXRD	FPD and FPCS	[149]
Pharmaceutical powder	Prediction of solid form composition of a particulate raw material	Raman spectroscopy and image analysis	Combination of data used in developing classification model	[150]
Pharmaceutical granules, polyester resins	Predictions of process concentration profiles	NIR and process variable sensors	Fused process and NIR information in MSPC models	[153]
Milk powder	Skimmed milk powder authenticity investigation	Hyphenating ultraviolet–visible, fluorescence and NIR spectroscopy	The fusion of the classification results	[154]
Coffee powder blends	Composition measurement of coffee blends	NIR spectroscopy and X-ray fluorescence (XRF)	Low-level and mid-levels	[155]
Coffee beans	Quality of fresh coffee beans	Digital olfation devises electronic nose analysis, tasting panel	Fusion of electronic devices in combination with the tasting panel	[156]
Ground roasted coffee	Discrimination between unadulterated and adulterated coffee samples	Mid-IR spectroscopy with different acquisition modes: Attenuated Total Reflectance (ATR), and Diffuse Reflectance (DR)	Data fusion to combine the data from DR and ATR	[157]
Wheat flour samples	Functional properties and quality of wheat flour	NIR and Mid-IR spectra	Low-level and mid-level data fusion	[158]
Agricultural powders	Determination of protein and starch content in agricultural powders	NIR and fluorescence spectroscopy	Low-level data fusion	[159]
Botanical powder samples	Differentiating the origins of Magnoliae Officinalis Cortex	E-nose measurements, e-tongue measurements, and chemical analyses	Low-level and mid-level	[160]
Clay powder samples	Clay mineral identification	Laser-induced breakdown and Raman spectroscopies	Low-level data fusion	[161]
Soil samples (silt to silt loam texture)	Soil aggregate stability prediction	Visible NIR (Vis-NIR) and Mid-Infrared (MIR)	Spectra fusion and model output averaging	[162]
Soil samples (paddy soil)	Evaluating soil fertility and quality	Vis–NIR, Mid-IR spectrometer, portable (XRF) analyser and Laser-Induced Breakdown Spectroscopy (LIBS)	Models using PLSR based on fused sensor data, and Bayesian Model Averaging	[163]
Soil samples with a wide range of soil texture	Assessment of soil bulk density	Frequency domain reflectometry and visible and NIR spectroscopy	PLS and ANN data fusion	[164]
Soil samples with a wide range of soil texture	Measurement of soil bulk density	Frequency domain reflectometry and Vis-NIR spectroscopy	ANN data fusion	[165]
Soil samples (soil textures ranging from sand to clay loam)	Characterization of the spatial complexity of soils	Gamma ray, electrical conductivity, Vis-NIR spectra	PLS Fusion of data	[166]
Polluted soil samples	Prediction of toxic elements in soil	Vis-NIR and X-ray fluorescence	Low-level and mid-level	[167]
Fine-grained sieved and homogenized soil samples	The compositional discrimination of geological materials	XRF spectroscopy, Raman spectroscopy, and LIBS	PCA and PLS-DA Mid-level	[168]
Soil samples of arable fields	Estimation of key soil attributes	Vis-NIR and XRF	Spectra fusion	[169]
Large variety of soil samples	Prediction of soil physical and chemical properties	Vis–NIR and portable XRF spectra	Mid-level	[170]
Soil samples collected from the cropland	Prediction of toxic elements in soil	Portable XRF and Vis-NIR sensors	Low- and Mid- and high-level fusion	[171]

application of diffuse reflectance in the Vis-NIR region to determine physicochemical attributes of dairy powders. Moderate to good performance was achieved for tapped density, insolubility index, surface free fat, moisture content and bulk density (R_P^2:0.65–0.88, 0.80–0.85, 0.77–0.87, 0.71–0.86 and 0.71–0.72, respectively). Therefore, prediction efficiency of physical attributes of some type of powders using only vibrational spectroscopy may not be adequate enough.

On the other hand, physical attributes of powders can be interpreted using other sensory instruments including acoustic emission profile as shown in Table 2. Hansuld et al. [50] showed that increases in particle size and density could affect the observed acoustic emission profile. Moreover, it was found that the flowability of bulk of powders could be determined using data from the acoustic emission [177,178]. In addition, both NIR and Ultrasonic Pulse Velocity were successfully implemented by other researchers to non-destructively estimate hardness [20,116]. Acoustic emission has the capability to monitor changes in physical properties of particulate materials while vibrational spectroscopic instruments could provide some information about chemical properties of powder materials and their spectral band variations at different conditions [175]. Coupling of these two techniques could therefore be a useful method for the estimation of physical attributes of powders such as particle size, flowability, bulk density and hardness.

For the measurement of physical properties of particles such as size, flowability and bulk density, several parameters can be determined using digital imaging technique and integrated to those data obtained from vibrational spectroscopy and acoustic emission. Adequate powder flowability characterisation technique for a

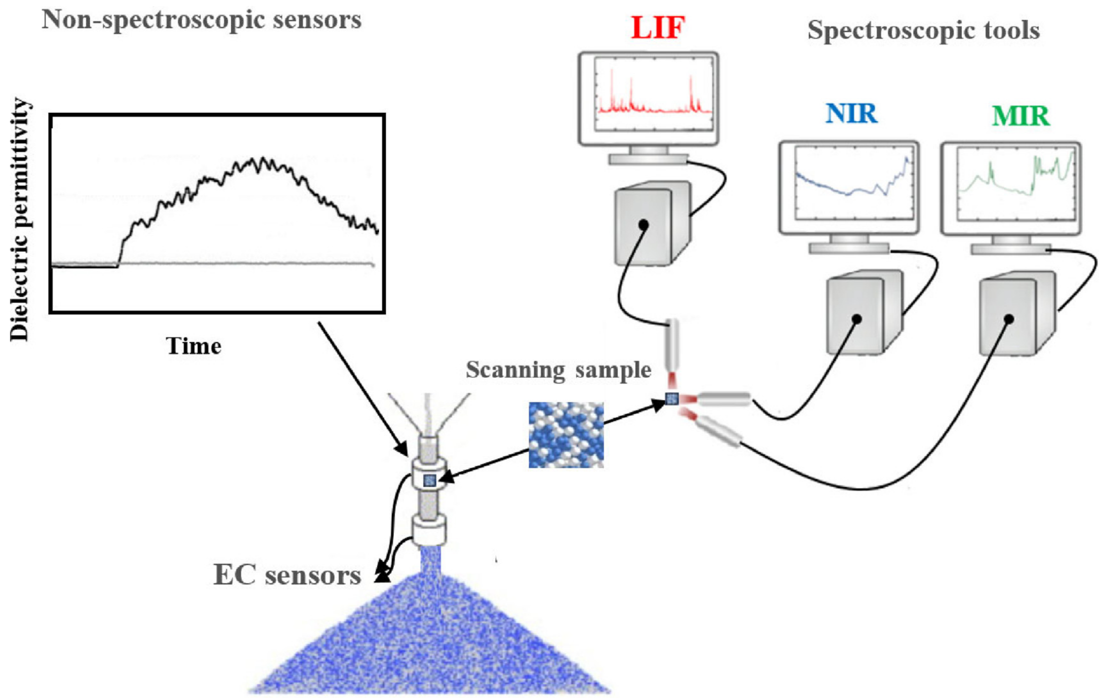

Fig. 12. Opportunity of the implementation of multi-sensors technology for composition and homogeneity assessment of powders.

powder-bed based metal additive manufacturing process based on digital imaging technique was investigated by Spierings et al. [56] which gave valuable information about the significance of inter-particle forces. Powder avalanche angles (angle of a linear regression of the free powder surface just before an avalanche started) and powder surface fractal (defined by the resolution of the recorded image (pixel size)) were evaluated using digital imaging and image processing techniques in a rotating drum. These parameters were shown to be correlated to optically evaluated flowability results obtained from an independent assessment of five experienced people. It can be expected that flowability will correlate with other powder properties such as powder layer density, particle size distribution and particles shape. These parameters can further be recorded and evaluated using digital imaging technique [52,179–183]. Overall, Fig. 13 schematically represents the opportunity of implementation of data fusion for vibrational spectroscopy such as NIR (which provides spectra data of absorbance by time), acoustic emission profiles (which provides the acoustic emission by time), and digital imaging tools (which evaluates the desired optical property by time). Data can be integrated using a low- or mid-level data fusion strategy, and compared for the final decision.

In Fig. 13, process variables have also been shown as a unique source of data which can potentially change the powder and granule properties. For instance, Ryckaert et al. [53] observed that the process variables including torque was an indication of the degree in granule growth, with the potential of being used as an in-process control parameter for granule size during twin-screw wet granulation. In another study, different approaches for moisture content monitoring based on soft sensor model development have been investigated by Roseberry et al. [184], where manipulated input process variables of a fluidized bed process were utilized to successfully develop models for moisture prediction. In terms of tablet hardness, Table 2 shows that the process variables could be successfully implemented for the prediction of tablet hardness. Thapa et al. [69] reported that impeller speed, liquid addition rate, and wet massing time could impact the granule hardness, Carr's index, tablet tensile strength in a high shear wet granulations. Thus, process data could be complementary to other in-line sensory information such as vibrational spectroscopy to evaluate the physicochemical attributes of an end-point powdered-based product such as particle size, hardness and moisture. Opportunities could be created to study the fusion results of collected sensory data from vibrational spectroscopy and process data (e.g. flow rate, temperature, pressure, impeller speed, torque) to investigate whether it could provide more accurate information and predictions with less uncertainty than an individual sensor in powder and granule production processes. For data fusion, spectral data, as an extra block of correlated variables, could be integrated to the process data measurements using data augmentation technique, or they can be treated as separate blocks of information, and processed individually to develop a final model using a multi-block analysis, [185] (Fig. 14). Vibrational spectroscopic systems such as NIR or Raman spectroscopy can be used as a spectral data block.

As previously shown in Table 2, vibrational spectroscopy such as NIR is a relatively suitable technique not only for the physical characterisation of powders (e.g., particle size, flowability, hardness and density), but also for the measurement of the moisture content. For moisture prediction, the opportunity of fusing the data of microwave sensors (Table 2) along with process and vibrational spectroscopic data can also be considered as microwave sensors diagnose a very good contrast between water and most other materials [115], which could potentially complement the results.

If acquiring spectral data from a process is not applicable, opportunities could be created to explore the feasibility of using morphology metrics along with process variables to develop an in-line/on-line approach for the prediction of physical properties of powders and granules (Fig. 15). For instance, flowability is an important quality indicator for many powdered products which is affected by not only process variables [186], but also the morphology of the powders [187]. Other model outputs can also be tested to check the feasibility of combining process and shape factors for predicting them. For instance, bulk or tap density, com-

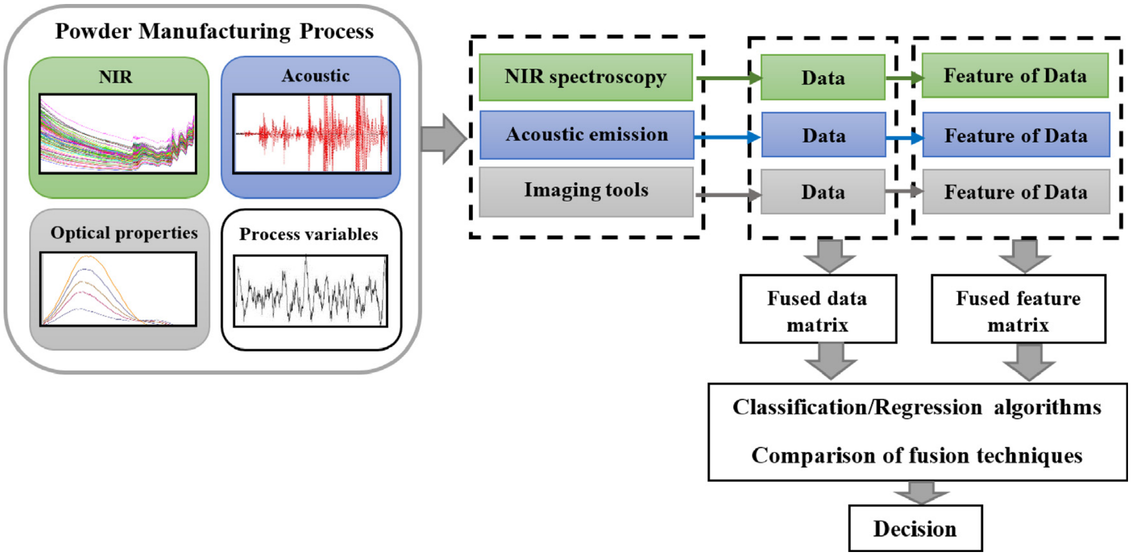

Fig. 13. Opportunity of the implementation of multi-sensors technology for the assessment of physical properties of powders such as bulk density, particle size, and flowability.

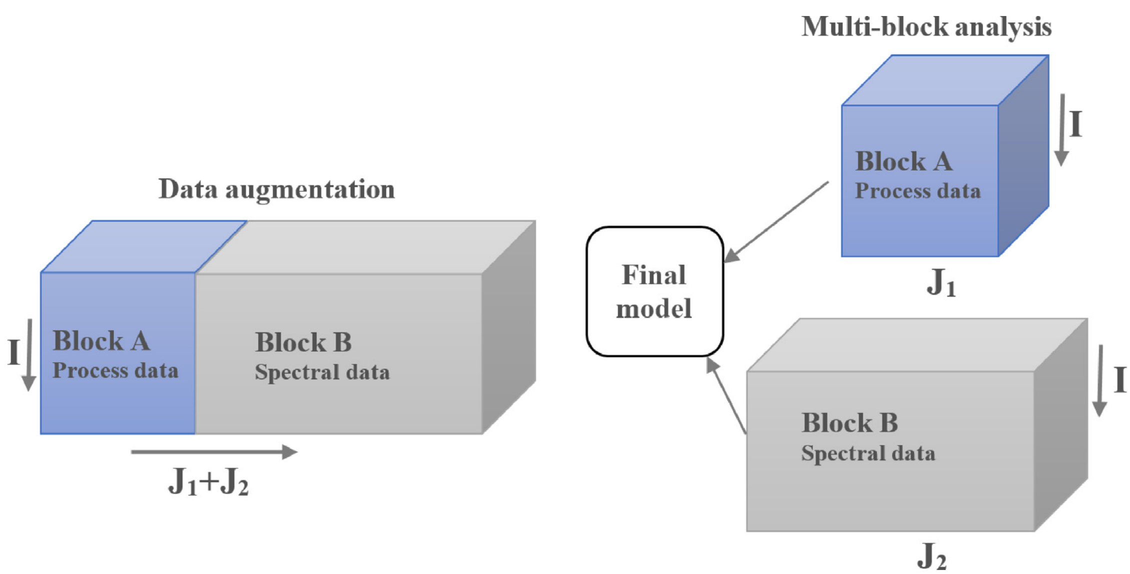

Fig. 14. Fusion of process and spectral data: I is time, J_1 is the number of variables for block A (process data) and J_2 is the number of variables for block B (spectra data).

pressibility, dissolution rate and tablet hardness in the case of pharmaceuticals can all be tested as model outputs (Fig. 15). In a recent study, Wang et al. [188] investigated the correlation between the powder particle morphology of microcrystalline cellulose and its tablet performance. Circularity was reported to be the most important shape factor affecting the tablet performance, which correlated well with tablet hardness and disintegration/dissolution rates [188]. It also affected the powder compressibility (the greater the circularity, the closer the particle shape to the spherical, and the lower the powder compressibility). Wang et al. [188] also concluded that the particle shape affected the powder flowability for the measured samples of interest.

Moreover, an opportunity can be created to indirectly predict difficult-to-measure variables from the information of existing real-time analysers measuring other quality attributes of powder products in a process (Fig. 16). As an example, bulk density can be reliably predicted by real-time measurement of particle size [189], moisture content [190] and process data (e.g. torque) [191] using MSMs [16] and different data fusion approaches. Size analysers and spectroscopic data could allow the clear distinction between different stages of a powder process. For instance, FBRM has been designed to measure real-time changes of particle size and distribution in the process by tracking the rate and degree of change to particle count and size. This technique is particularly important for harsh condition processes. In high shear wet granulation processes, materials may be adhesive and are prone to get sticky during granulation stage causing probe fouling. Based on advanced FBRM design, a mechanical scraper could be utilized on the sapphire window to prevent probe fouling [192]. Therefore, combining of a size analyser such as FBRM (for the measurement of PSD, D90, D10 and D50), vibration spectroscopy such as NIR (for the measurement of moisture content) and process data such as torque (for the measurement of system power), and integration of all the real-time data could facilitate determination of the bulk density of powdered-based products. It should be stated that the number of variables could be significantly different for spectro-

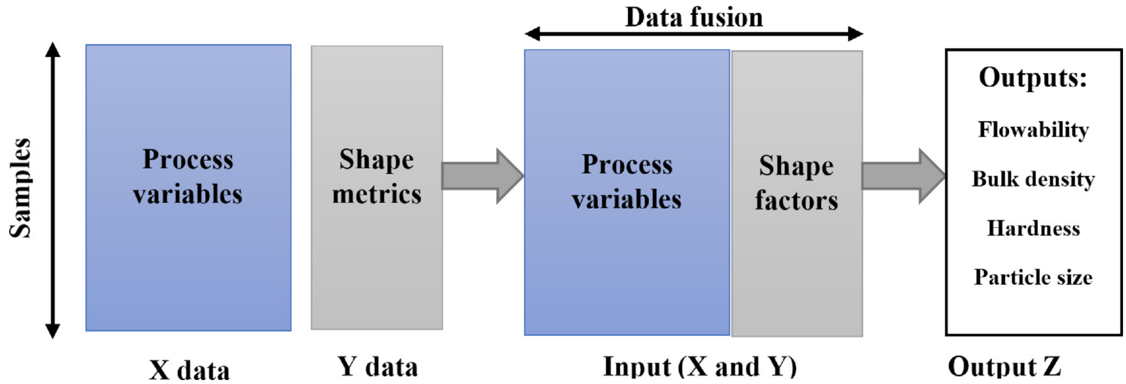

Fig. 15. Opportunity of the implementation of process variables and shape metrics for developing a predictive model for estimating physical properties of powders/granules.

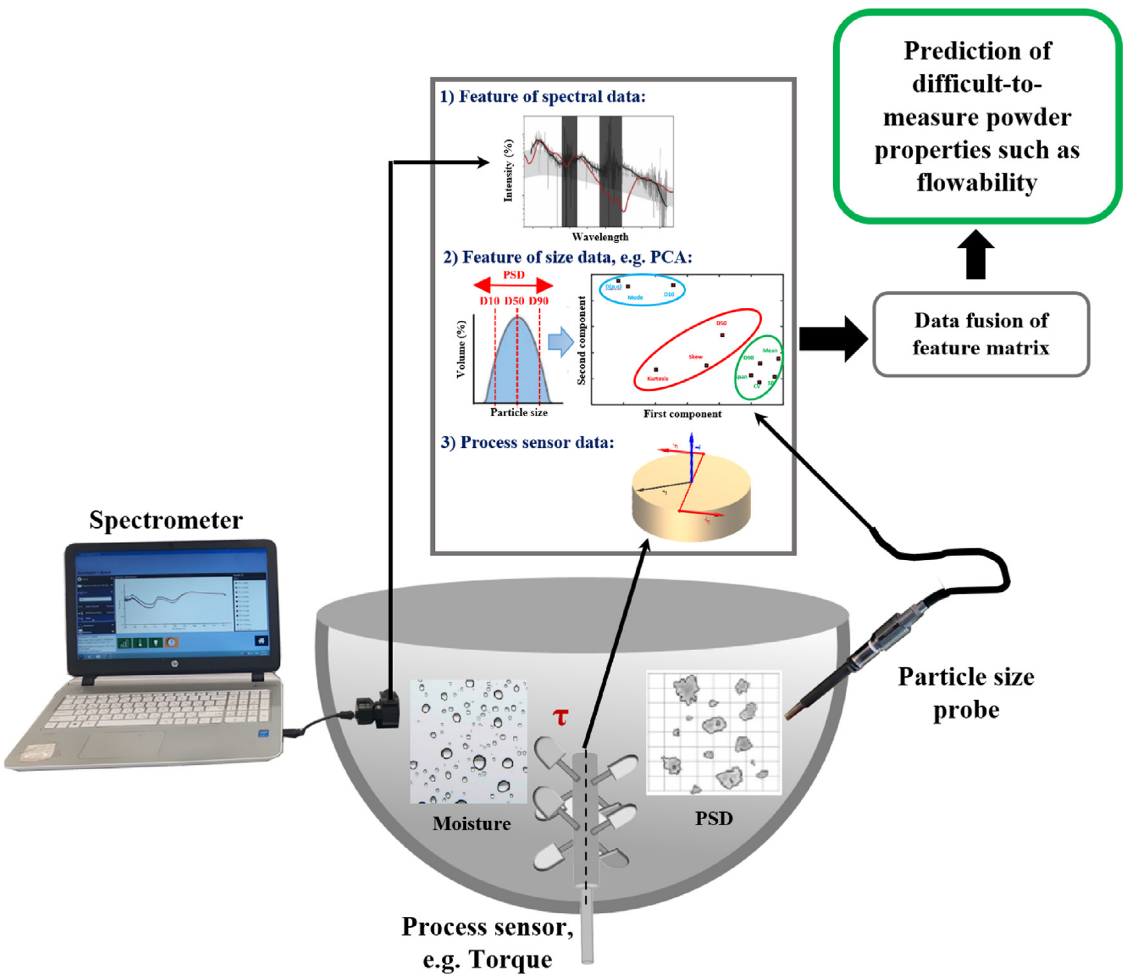

Fig. 16. Opportunity of the data fusion of process sensors, particle size analysers and spectral data for predicting difficult-to-measure physical properties of powders/granules (Images licenses:"Near-infrared spectrum of EM170817 at 4.5 days after binary neutron star merger" by M. M. Kasliwal et al., is licensed under Creative Commons Attribution 2.0 Generic license."Work-torque" by Svjo is licensed under Creative Commons Attribution-Share Alike 4.0 International license.).

scopic, FBRM and process datasets. In this case, data fusion based on a mid-level approach should be potential as it could provide a more balanced representation of variability captured in datasets. Therefore feature selection techniques may be suitable here to extract the valuable variables of particle size in size analyser and spectra in spectroscopy, to complement the low dimension process dataset. Another example of a difficult-to-measure variable is powder flowability. It depends on particle lubrication, particle size and moisture content [94,193]. To this respect, the combined use of a vibrational spectroscopy and a size analyser/image analysis tool can be highly beneficial for a data fusion application. Vibrational spectroscopy such as NIR could accurately predict the lubrication and moisture content of particles, whereas the size analyser/image analysis tool could provide accurate particle size distributions. Fusing these data can potentially deliver a more accurate estimation of flowability compared to a single instrument.

Finally, potential advantages of saving both experimental time and cost can be achieved if a number of literature data and material database from historical datasets merged into the obtained collected data at laboratory. Wang et al. [194] demonstrated that incorporating a small number of literature data into the multivariate calibration model could help significantly reduce the prediction error in a high shear wet granulation process for manufacturing of oral solid dosage.

4.2. Multi-minisensors as an alternative for expensive sensors data fusion

Normally, monitoring and controlling of CQAs are performed using expensive in-line or on-line analysers or time-consuming off-line/at-line techniques in a continuous process. Thanks to advances in technology today, miniaturised yet inexpensive sensors reached to mass production. As an instance, Fig. 17 shows how NIR spectroscopy has been evolved from being expensive and massive in size to a cheap and portable equipment. Therefore, in-line miniaturized analytical instruments could be embedded within the system and used along with the process sensors to acquire the complementary data for monitoring CQAs. Yin e al. [195] reviewed the soil sensors for smart and precision agriculture application which enable capturing real-time physical and chemical signals in the soil, such as temperature, moisture, pH, and pollutants. Miniaturized sensors for smart and precision agriculture including miniaturized wireless system for sensing soil water content and conductivity, on-chip piezoresistive soil temperature sensor and miniaturized optical moisture sensor [195] could potentially be designed and investigated for characterising other powder mixtures. Principles and applications of miniaturized NIR Spectrometers [196], miniaturization of fluorescence sensing [197], and other optical spectrometers [198] could also give valuable insights on the minimization opportunities for spectroscopic instruments which could revolutionize the powder manufacturing processes.

4.3. Data fusion for real-time monitoring and control schemes of CQAs

Study on real-time process monitoring, fault detection scheme and process control using prediction models build on data fusion techniques is an area that lacks sufficient investigations and has the potential to be implemented within a continuous system to monitor and control the quality of powdered and granule products (Fig. 18). Developing a robust soft-sensor from multi-sensors can be used as a backup sensor when the hardware sensor is in fault or removed [200]. In this case, if one sensor is malfunctioned during the process, monitoring and controlling of the process is feasible using the developed soft sensor. Therefore, measurements by various process sensors, in-line PAT and applying an efficient data fusion approach could not only allow detection of faulty operation of a system in real-time, but also precise control and optimisation of complex processes.

By adopting advanced control techniques, such as Model Predictive Control (MPC), process constraints and multivariate interactions can be taken into account in the process [201]. The MPC control scheme could manipulate the manipulated variables to control a CQA to its desired set-point which could be predicted from an efficient MSM and data fusion approach (Fig. 19). After some initial online tuning, the MPC could be able to control a CQA to its desired set-point by manipulating the manipulated variables in the process. Therefore, finding an accurate data fusion

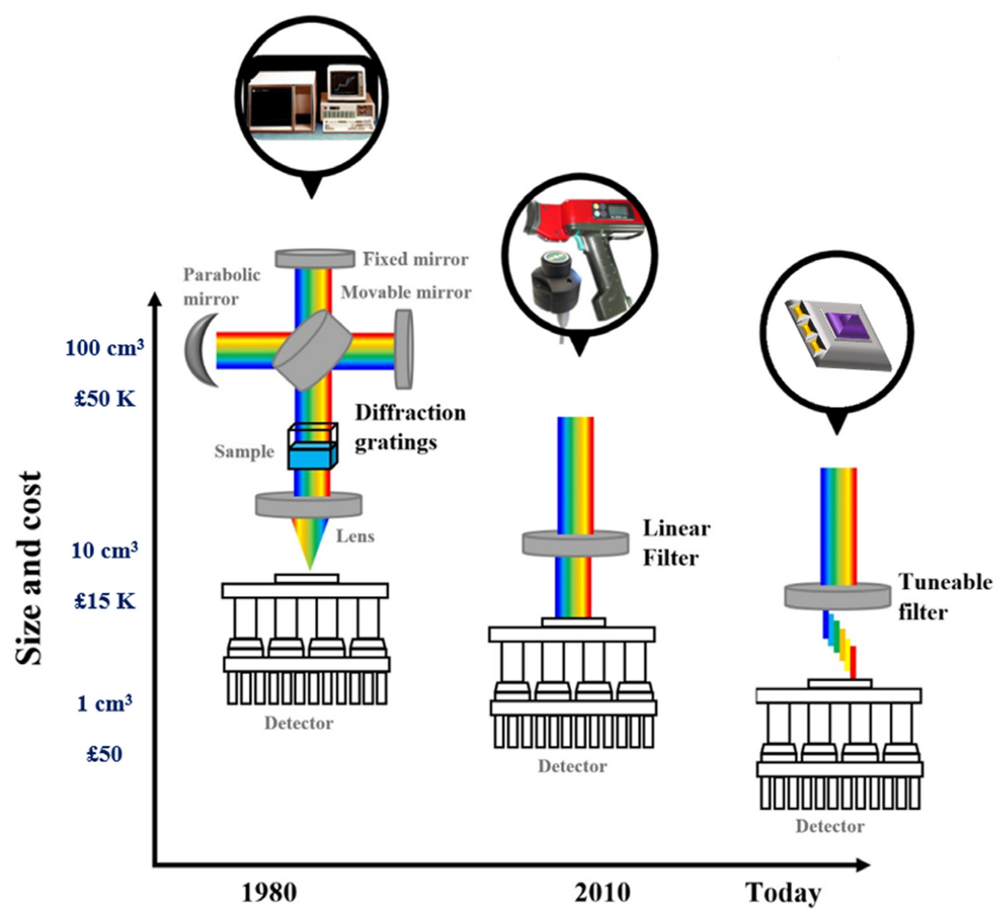

Fig. 17. Substitution of analytical instruments with cheap/miniaturized sensors in PAT platforms, [198,199].

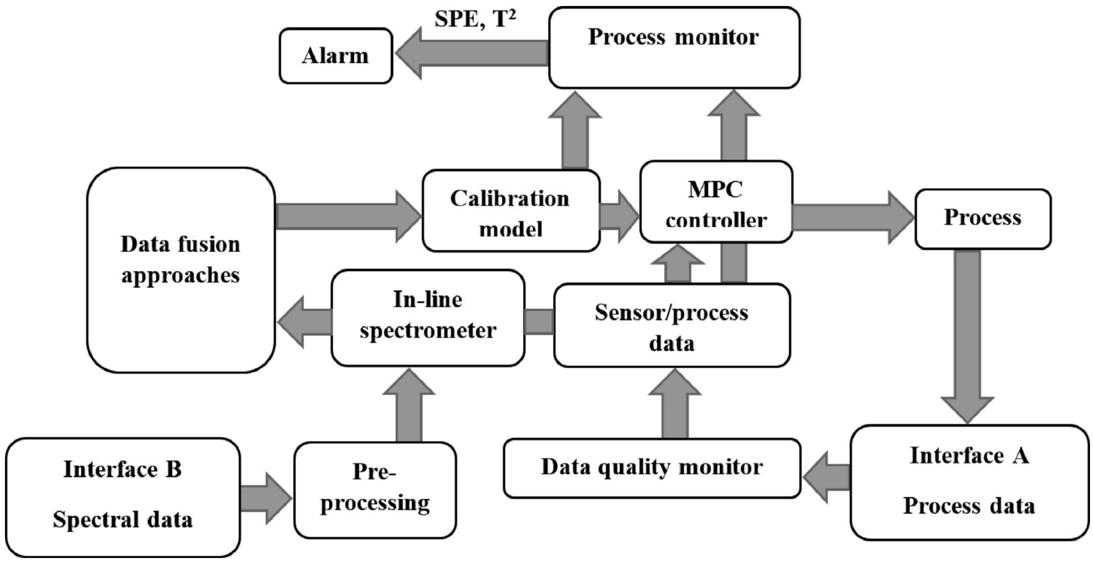

Fig. 18. Implementation of multi-sensors data fusion (in this case fusion of process and spectral data) for process monitoring and control schemes.

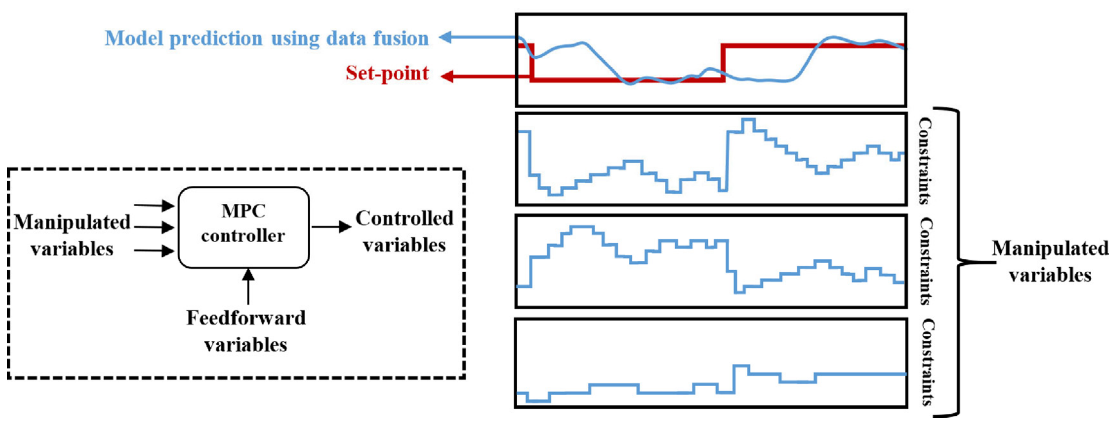

Fig. 19. Controlling a CQA to its set-point based on an MPC model.

approach to precisely predict the CQA is an important prerequisite to develop a robust MPC model, particularly for the cases when a suitable hard sensor is not available, malfunctioned or removed from the process. A PCA monitor model can also be developed based on data fusion calibration model and other process data for obtaining Hotelling's T^2 and Squared Prediction Error (SPE) metrics, to accurately detect faults within the system (e.g. probe/sensor faults, feeding issues, powder impurities/degradation, heater fault, etc.) [151].

One opportunity that can be created for developing a robust MPC model based on multi-sensors data fusion is investigation of the potential of spectral data fusion with other sources of data (shape metrics and process variables) (refer to section 4.1) to predict various physicochemical properties of powders during manufacturing processes. Overall, models could be constructed from (a) process variables only, (b) shape metrics variables only, and (c) spectroscopic instruments variables only, and (d) process variables combined with shape factors and spectroscopic variables, and compared to evaluate the most important variables in developing soft sensors for predicting the CQAs. The same approach as De Oliveira et al. [153] could be investigated for the development of SPC and PCA monitor models by combining the collected data. De Oliveira et al. [153] combined all the available process related information along with spectroscopic data to develop a robust SPC model and concluded that an accurate data fusion methodology has a high performance at detecting on– and off-specification batch situations, and identifying the sources of process abnormalities.

5. Conclusions

Today's processes implement many sensors and analytical instruments which can provide more information and opportunity to monitor, control and optimize CQAs. This correspondingly increases the complexity of the systems in terms of interpreting the data to capture process understanding. While data acquisition process can be achieved much faster due to progress in instrumental methods, interpretation of data and data analysis process still demand long time. Data fusion strategies can be utilized for the performance improvement of PAT platforms to facilitate exploiting the advantages of datasets created from various sources while improving the model accuracy and robustness. By adopting an efficient data fusion technique and integrating various datasets generated from multiple sources, more useful knowledge about a sample could be obtained than using a single source instrument. In this paper, current status and future perspectives regarding the application of multi-sensors data fusion for accurate in-line measurement and on-line controlling of CQAs in powdered and granule products were discussed. Some ideas regarding the integration of multi-sensors data using different data fusion approaches were proposed with the hope to improve the model performance for assessing a wide range of CQAs. Finally, the possibilities of real-time process monitoring, fault detection and process control schemes using prediction models build on data fusion techniques were described. Overall, calibration models developed for an accurate real-time prediction of CQAs based on multi-sensors data fusion, designing a robust MPC and process monitoring schemes to control CAQs to the desired set-points, and detecting process faults based on data fusion are among important research areas that could have a high impact on the quality assurance of powdered and granule products.

Data statement: No data are associated to this journal paper.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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