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Review

Overview of PAT process analysers applicable in monitoring of film coating unit operations for manufacturing of solid oral dosage forms

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ABSTRACT

Over the last two decades, regulatory agencies have demanded better understanding of pharmaceutical products and processes by implementing new technological approaches, such as process analytical technology (PAT). Process analysers present a key PAT tool, which enables effective process monitoring, and thus improved process control of medicinal product manufacturing. Process analysers applicable in pharmaceutical coating unit operations are comprehensibly described in the present article. The review is focused on monitoring of solid oral dosage forms during film coating in two most commonly used coating systems, i.e. pan and fluid bed coaters. Brief theoretical background and critical overview of process analysers used for real-time or near real-time (in-, on-, at- line) monitoring of critical quality attributes of film coated dosage forms are presented. Besides well recognized spectroscopic methods (NIR and Raman spectroscopy), other techniques, which have made a significant breakthrough in recent years, are discussed (terahertz pulsed imaging (TPI), chord length distribution (CLD) analysis, and image analysis). Last part of the review is dedicated to novel techniques with high potential to become valuable PAT tools in the future (optical coherence tomography (OCT), acoustic emission (AE), microwave resonance (MR), and laser induced breakdown spectroscopy (LIBS)).

1. Introduction

In 2004, Food and Drug Administration (FDA) launched a new initiative called “Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach” (FDA, 2004a). FDA's goal was to enhance and modernise the regulation of pharmaceutical manufacturing by encouraging pharmaceutical industry to adopt new technological advances, risk-based approaches, modern quality management techniques and at the same time ensure regulatory review and regulatory programs in line with the state-of-the-art pharmaceutical science (FDA, 2004b; FDA, 2004a). A key technological element of the FDA's initiative is Process analytical technology (PAT), which is defined as a system for designing, analysing, and controlling manufacturing through timely measurements of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality (FDA, 2004b). PAT initiative defines four groups of PAT tools: Multivariate tools for design, data acquisition and analysis, Process analysers, Process control tools, and Continuous improvement and knowledge management tools. Individual PAT tools are inter-connected and their simultaneous use and management is necessary for full integration of the PAT in the pharmaceutical industry, which was nicely illustrated in some recent studies (Obregón et al., 2013; Singh et al., 2014). The present article offers a comprehensive overview of PAT process analysers in the monitoring of film coating unit operations, since review of all four PAT tool categories is beyond the scope of this paper. Process analysers provide large volumes of data by (non-destructive, multivariate) measurements of critical process and material attributes. They can be differentiated into three groups: at-line (sample is removed from the process stream, measurement is taken in the proximity), on-line (sample is removed from the process stream, but may be returned after the measurement), and in-line (sample is not removed, since measurement is made directly in the process stream) analysers. Considering the essence of the PAT, in-line measurement is an ideal process analyser, since it enables multivariate, non-destructive, and rapid measurement in real time, generating large volumes of data. However, a lot of modern in-line technologies are still not tested and investigated enough in harsh process stream conditions and users are often faced with different technical difficulties and poor data quality. Therefore, in-line analysis should not be a priori considered as an optimum PAT solution as suggested by several recent scientific publications. Process measuring location and approach should be thoughtfully defined for each individual case based on both characteristics of the

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process and selected measuring technique.

PAT is especially applicable in case of complex pharmaceutical technological processes where small deviations of critical process parameters can lead to reduced or altered product quality. Film coating of solid dosage forms is one of such processes. Solid oral dosage forms are film coated for decorative (improved appearance, easier identification), protective (providing barrier to environmental and physiological factors, improved physical resistance), patient compliance (taste and odour masking, easier swallowing), and functional reasons (alter the release characteristics of drugs) (Felton, 2007). Film coating unit operations are most commonly performed in fluid bed coaters or pan coaters, where the former is more appropriate for coating of smaller dosage forms, such as granules, pellets, and mini-tablets and the latter is first option for film coating of bigger dosage forms, such as tablets. It is very important, especially in case of functional film coatings, which have direct impact on biopharmaceutical drug properties, to continuously provide film coating with targeted coating thickness and coherence (Shao et al., 2002). The amount of applied polymer during the spraying stage is most important for achieving targeted coating thickness, while adequate coating coherence (adequate coalescence of polymer particles) is achieved by efficient control of spraying stage process parameters, suitable film coating composition, and by proper post-spraying phase polymer treatment, named curing (Hamed and Sakr, 2003; Keddie, 1997; Williams and Liu, 2000). Besides average coating thickness of the entire population, inter- and intra- coating thickness variability are very important characteristics of film coated dosage forms. Inter-tablet coating variability is coating thickness variation between individual units, while intra-tablet variability is coating thickness variability over the individual unit's surface. Poor coating uniformity can lead to reduced coating functionality and problems, such as dose dumping, inadequate gastro-resistance, poor appearance, reduced stability etc. Thus, it is very important to produce dosage forms with low inter- and intra-coating variability (Kalbag and Wassgren, 2009; Freireich et al., 2015). Gloss and roughness of the coating are properties that are not directly related to its functionality. Nevertheless, they are important appearance attributes of film coated dosage forms, which can affect patient's compliance (Rowe, 1985). Glossy coatings with highly smooth surface reflect most of the incident light, whereas matte coatings exhibit some level of roughness, scatter part of the light and consequently reduce the gloss level (Valdesueiro et al., 2017). Therefore, both parameters can also affect the course of in-process measurements based on scattering and/or reflection of electromagnetic radiation (see Section 2 Near infrared spectroscopy). Film coating in pan and fluid bed coaters is a process influenced by many process parameters, such as inlet air temperature, inlet air flow rate, inlet air humidity, coating dispersion spray rate, product temperature, atomising pressure, coating pan speed, machine fill level, shape of dosage form etc. The number of process parameters gets even higher if curing is performed after the spraying step. Moreover, it must be taken into consideration that different process parameters are interdependent and not directly linked to final product properties, which makes efficient process control even more difficult.

Despite many challenges in film coating process, traditional pharmaceutical industry manufactures film coated dosage forms with mainly predefined and fixed process parameters irrespective of the real-time coating properties. Film coating properties are evaluated after the coating stage is finished by simple in-process control tests (e.g., sieve analysis) or they are evaluated only indirectly (e.g., through dissolution, appearance, gastro-resistance properties) as part of the final release specification testing. Testing at this stage is often too late, since entire inadequate batch must be discarded at the cost of the manufacturer. On the other hand, PAT process analysers enable measurement of critical attributes in real time, allowing immediate adjustment of critical process parameters. Timely process correction, according to detected coating deviation, increases the probability of production of medicine in line with the prescribed specifications. Therefore, the use of PAT process analysers can bring many benefits in design, evaluation, and control of film coating processes.

Present article reviews available PAT process analysers in the monitoring of film coating unit operations. More specifically, review is focused on monitoring of film coating processes for the preparation of coated pellets and tablets in fluid bed and pan coating systems. Process analysers discussed in the sections below are applicable for in-process measurement of a variety of critical quality attributes. Evaluated attributes can be primarily a consequence of sprayed quantity, i.e. coating thickness, pellet size, coating growth/weight, active ingredient content, can be more related to other critical process parameters, i.e. moisture content, residual solvent content, degree of agglomeration, coating uniformity, or can be a result of the entire course of the film coating stage, i.e. drug release, gastro-resistance, appearance. The article is primarily focused on analysers capable of real-time or near real-time monitoring (in-, on-, and at-line), meaning that the measurement is rapid enough to allow immediate adjustment of the on-going process operation, which is the ultimate goal of the PAT. Off-line measurement is mentioned in the article, if it is clear from the cited reference that the method allows determination of critical quality attribute in time which still permits efficient process control, meaning that with some adjustments the measurement could also be used as in-, on- or at-line analyser. For example, study of (Wirges et al., 2011) is listed in the Table 2, although the study was carried out in off-line mode, since it is clear from the article that measurements was rapid (15 s), non-destructive, and was capable to predict active ingredient amount in the samples with different quantity of the active coating applied. In addition, off-line measurement can be mentioned in this review, if the cited article is important for understanding the presented measuring principle or its background. Brief theoretical background, working principle, and critical overview of individual technique's applicability is discussed from Sections 2 to 5. In addition, tabular overview of studies investigating PAT analysers in the monitoring of film coating unit operations is made to summarize their applicability (refer to Table 1 for NIR spectroscopy, Table 2 for Raman spectroscopy, and Table 3 for terahertz pulsed imaging and particle size analysis). Section 6 Other process analysers offers a review of four less recognized process monitoring approaches, which show potential to become valuable PAT tools in the future. The criteria for their selection is discussed in the beginning of Section 6.

2. Near infrared spectroscopy

Near infrared (NIR) spectroscopy investigates the absorption of electromagnetic radiation in the wavelength range from 700 to 2500 nm (wavenumber from 14,300 cm^{-1} to 4000 cm^{-1}). NIR region is situated before the mid infrared region (2500–10,000 nm) and far infrared region (10–1000 μm) (De Beer et al., 2011). Although the region was discovered by German musician and astronomer Frederick William Herschel in 1800 already (Herschel, 1800), the breakthrough of NIR application happened only in the second half of the 20th century when agricultural engineer Karl Norris successfully applied statistical methods for calibration of NIR data (Norris and Hart, 1965). In NIR spectroscopy, samples are irradiated with NIR light which brings molecules to a higher vibrational state when NIR radiation is absorbed. NIR light is absorbed only when induced vibration results in the change of molecule's dipole moment (Fig. 1). Therefore, two-atomic molecules require a permanent dipole to be IR active, while larger molecules with polyatomic structure require a dipole induced by vibration. O—H, N—H, C—H, and S—H bonds are known as strong NIR absorbers, since their dipole moment is high. On the other hand, H_2 does not absorb NIR radiation because no change in a dipole moment occurs during its vibration. Absorption of the radiation can lead to vibration in 2 modes: stretching and bending. Stretching presents continuous change in the interatomic distance along the bond axis, while bending presents a change in bond angle (De Beer et al., 2011). In the literature NIR spectroscopy is often related to vibrational transitions only. However, it

Table 1
Studies investigating applicability of NIR spectroscopy in monitoring of film coating unit operations for manufacturing of solid oral dosage forms.

Dosage form	Attribute	Process	Measurement	Reference
Tablets	Coating thickness	Pan coating	In-line	Pérez-Ramos et al., 2005 Römer et al., 2008 Gendre et al., 2011b
		Fluid-bed coating	In-line	Lee et al., 2010
	Weight gain	Pan coating	In-line	Gendre et al., 2011b Möltgen et al., 2012
	Moisture content	Pan coating	In-line	Möltgen et al., 2012
	Curing progression	Static curing	Off-line	Tabasi et al., 2008 Gendre et al., 2013
		Dynamic curing in pan coater	Off-line	Gendre et al., 2012 Gendre et al., 2013
	Drug release	Static curing	Off-line	Tabasi et al., 2008
		Pan coating	In-line	Gendre et al., 2011a
Pellets	Coating thickness	Fluid-bed coating	Off-line	Marković et al., 2014
			At-line	Avalle et al., 2014 Korasa et al., 2016
			In-line	Andersson et al., 2000 Lee et al., 2011 Hudovornik et al., 2015
	Sprayed quantity	Fluid-bed coating	In-line	Bogomolov et al., 2010 Marković et al., 2014
	Active ingredient content	Fluid-bed coating	At-line	Avalle et al., 2014
	Pellet size distribution	Fluid-bed coating	In-line	Marković et al., 2014
	Acidic resistance	Fluid-bed coating	In-line	Marković et al., 2014
	Moisture content	Fluid-bed coating	In-line	Bogomolov et al., 2010 Hudovornik et al., 2015
	Residual solvent content	Fluid-bed coating	In-line	Marković et al., 2014
	Curing progression	Dynamic curing in fluid bed coater	At-line	Korasa et al., 2016
	Drug release	Fluid-bed coating	At-line	Avalle et al., 2014
			In-line	Pomerantsev et al., 2011
		Dynamic curing in fluid bed coater	At-line	Korasa et al., 2016

must be pointed out that lower wavelength of the NIR region, i.e. in the range 700 nm to 1200 nm, can also result in electronic transitions. This NIR region can be called as “the window of body” since its high transparency, which makes it useful in a number of biomedical applications (Ozaki, 2012). Nevertheless, molecular vibrations, such as overtones and combinations of fundamental vibrations caused by NIR absorption, remain the main reason for high applicability of the NIR spectroscopy as a PAT tool.

NIR spectroscopy has many advantages, which make it the most commonly used PAT process analyser in pharmaceutical technology. NIR spectroscopy can make non-destructive measurements in a very short time, making generation of large volumes of data in real-time possible. In addition, optical fiber probes enable diffuse reflectance measurement of samples in various states and shapes directly in the process stream. Diffuse reflectance is preferred and most frequently applied mode for in-process measurement of solid dosage forms. Thus, all studies listed in Table 1 were conducted using diffuse reflectance technology. Finally, NIR spectrum can give information about a great number of process variables simultaneously, which makes this process monitoring tool an ideal PAT process analyser (De Beer et al., 2011; Jamrógiewicz, 2012; Ozaki, 2012). Nevertheless, NIR spectroscopy also has its drawbacks. Firstly, calibration of spectral data with the reference method must be done prior to monitoring of individual process. Such calibration is time consuming and requires specific knowledge of multivariate data analysis and spectral pre-treatment to exploit NIR's full potential. Secondly, NIR spectroscopy is extremely sensitive to moisture content. This characteristic enables accurate and precise water quantity evaluation, but at the same time it can cause troubles when measuring other critical quality attributes. High sensitivity of NIR measurement to water content was confirmed in some recent studies (Hudovornik et al., 2015; Korasa et al., 2016). Moreover, intra- and inter- coating variability is typically not measured with the in-line NIR spectroscopy due to moving of the tablets/pellets during the process, too long averaging time of the measurement, and the fact that volume of the sample measured by diffuse reflectance process analysers is greater than one dosage unit. The same applies for the Raman spectroscopy, which is described in the following section. However, Andersson et al. (1999) showed that at-line NIR measurement of individual tablets, using a

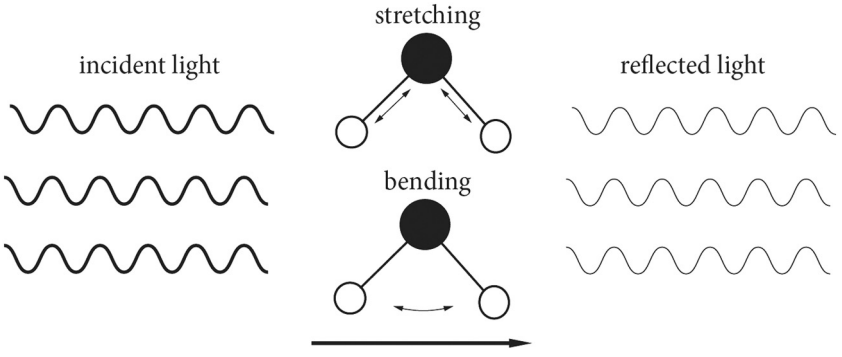

Fig. 1. NIR light is absorbed when vibrations of the molecule (stretching or bending) result in a molecular dipole moment change.

tablet holder, allows determination of inter-tablet coating homogeneity and thickness variation between both tablet sides.

There are several studies investigating the applicability of NIR spectroscopy in the monitoring of film coating process. The reason for this is that NIR spectroscopy can detect and measure virtually any critical quality attribute that is directly or indirectly linked to any spectral variation caused along the coating process. Most of the published studies investigate spectral variation as a consequence of compositional (chemical) change in the monitored area, since changing of the surface's composition during the coating process usually leads to high spectral variation, which makes a good basis for calibration of the NIR data with the reference method. On the other hand, the proportion of undesired physical scattering (caused by material movement, temperature variation, density variation etc.) is rather high in case of real-time measurement, which makes physical NIR information less applicable for real-time evaluation of the coating process. A thorough review of the NIR in pharmaceutical film coating applications was made by Knop and Kleinebudde (2013), so only a short summary of studies already mentioned in their article is presented below and comprehensive discussion is dedicated to recent studies and research areas not referred to in their review article. Summary of the studies investigating applicability of NIR spectroscopy in monitoring of film coating unit operations is presented in Table 1.

Research articles investigating film coating of tablets show high potential of in-line NIR for the evaluation of multiple tablet characteristics. Applicability of the in-line NIR in the measurement of tablet coating thickness was first shown by Pérez-Ramos et al. (2005), who introduced univariate analysis for modelling film coating growth, and Römer et al. (2008), who calibrated a multivariate PLS model using a small rotating plate coating system and used the model to predict coating thickness in a lab scale coating drum. Later research of Lee et al. (2010) showed that averaging of NIR spectra and PCA-based clustering can improve R^2 of PLS model for coating thickness prediction. Gendre et al. (2011b) showed that real-time monitoring of film thickness and mass of coating materials applied is possible. Real-time coating growth quantification was also demonstrated by Möltgen et al. (2012), who simultaneously determined another critical tablet characteristic, moisture content. In addition, it was shown that PCA of the NIR data enabled visualization of the entire coating process in one plot. A big step forward was made by the study of Gendre et al. (2011a), in which researches carried out real-time prediction of drug release in three time points (at 4 h, 8 h, and 12 h) of the sustained release coated tablets. In-line NIR spectroscopy is also very useful in the development and manufacturing of film coated pellets. Andersson et al. (2000) measured film coating thickness of pharmaceutical pellets inside a fluid bed chamber with NIR diffuse reflectance fiber-optic probe and showed good predictability of such approach (PLS model, $R^2 = 0.97$, root-mean-square error of calibration = 2.2 μm). Very good coating thickness prediction was also presented by Lee et al. (2011). The authors correlated NIR spectra with confocal laser scanning microscopy and with laser diffraction particle size analysis using the PLS regression. Possibility of sprayed quantity evaluation and moisture content determination with NIR spectroscopy was demonstrated by Bogomolov et al. (2010), who also investigated the effect of NIR and Raman data augmentation on the quality of delivered process-relevant information. Pomerantsev et al. (2011) developed a method for the prediction of drug release from Acryl-EZE film coated pellets, using a combination of the kinetic model and PLS regression. Their research showed high potential of in-line NIR technology in the production of functionally film coated pellets.

More recent studies investigating the applicability of NIR spectroscopy in the film coating were focused on the evaluation of multiple pellet characteristics simultaneously. In their study, Avalle et al. (2014) developed at-line NIR control strategy for evaluation of critical quality attributes of both active ingredient layer and controlled release layer. Firstly, PLS models for the prediction of active ingredient layer thickness and active ingredient content were set. Both models were consistent with off-line reference measurements. Secondly, the researchers developed PLS models that were capable to predict controlled release coating thickness and time required to release 80% of the active ingredient ($T_{80\%}$). In-line NIR monitoring approach for measuring key pellet characteristics was also developed by Marković et al. (2014), who calibrated PLS models for pellet size sieve fraction, residual solvent content, and amount of coating layer evaluation. In addition, hierarchical PLS model for acidic resistance determination was successfully constructed. Wide applicability of in-line NIR spectroscopy in the monitoring of pellet coating was also described by Hudovornik et al. (2015). The authors claimed that NIR probe could be used as a single tool for monitoring water content, sustained release coating thickness, and for detecting process errors such as pellet abrasion. Moreover, researchers showed that NIR spectroscopy was capable to predict moisture content in pellets with altered coating composition. All above presented studies suggest high applicability of the NIR technology for evaluating multiple critical quality attributes over the course of coating process in real-time.

As mentioned in the Introduction section of the present article, curing is a critical process step for achieving targeted biopharmaceutical properties of controlled release dosage forms. Tabasi et al. (2008) linked the extent of curing of Eudragit® RL:RS coated tablets with the convergence of the 1908 nm peak. Furthermore, the authors presented 7-factor PLS model for the prediction of the amount of theophylline released at 250 min. As well as Tabasi and co-workers, reduction of the 1908 nm peak due to curing phenomenon was also observed by Howland and Hoag (2013). However, 1908 nm peak is situated in the direct proximity of the broad water band region at 1940 nm, and thus its suitability for curing monitoring is rather limited, which was also shown in our recent study (Korasa et al., 2016). Nevertheless, the findings of the study suggested that the extent of curing could be determined with the at-line NIR analyser and that the prediction of diclofenac drug release rate from prolonged release coated pellets (Eudragit® RL:RS) was possible, using the PLS model based on talc and diclofenac sodium peaks (Fig. 2). Such results show that NIR could be applicable technique for detection and quantification of the curing phenomena and could provide useful monitoring tool for real-time drug release prediction and control. However, the prediction of drug release rate was not possible in case of high moisture content, although the PLS model was not based on the 1908 nm peak. Curing process was also investigated by Gendre et al. (2012) and Gendre et al. (2013), who detected variation of two characteristic water bands, i.e. 5060–5380 cm^{-1} and 6970–7190 cm^{-1}, which suggested that spectral variation correlated with the removal of water trapped within the coating. However, no spectral variations directly linked to curing of ethyl cellulose coated tables were observed. All in all, applicability of the NIR spectroscopy for monitoring of the curing phenomenon is rather unexplored and further research is needed to provide approaches less susceptible to water content variation and to develop industrially applicable models for drug release rate quantification.

Hereinabove listed studies suggest that NIR spectroscopy is most widely used PAT process analyser in design, monitoring, and control of film coating process. Nevertheless, this PAT approach still has a lot of aspects that must be investigated in greater detail. Curing phenomenon is definitely one of them. Furthermore, additional research should be carried out to elucidate the effect of water content fluctuations on determination of individual critical quality attributes and to determine whether developed models are applicable in cases when high moisture content is present in the analyte. Since the NIR spectroscopy is highly sensitive to moisture, this aspect is very important for pharmaceutical industry which faces a variety of different process environments. Moreover, novel spectral pre-treatment options and model calibration approaches should be evaluated. Most of the above listed studies used the same set of spectral pre-treatments, such as multiples scatter correction (MSC), standard normal variate (SNV), and first/second

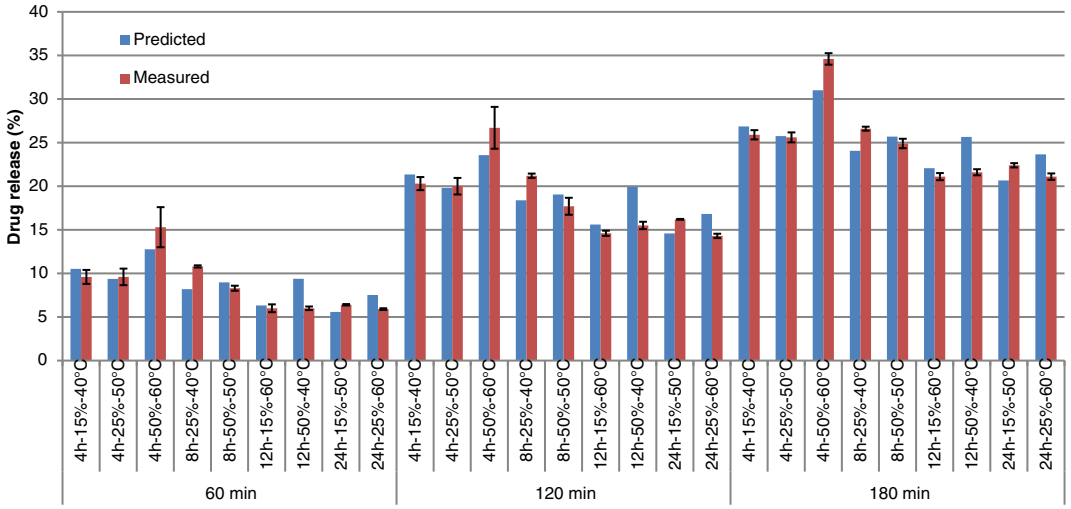

Fig. 2. The results of the drug release rate in different time points (i.e., after 60 min, 120 min, and 180 min), measured with the reference dissolution method and predicted with the at-line NIR approach, showed that NIR spectroscopy can be a useful tool for monitoring of prolonged release pellets curing process (sample name is defined by the curing conditions in the form Time-Relative humidity-Temperature). Error bars represent standard deviation of drug release measurements. This figure is taken from Korasa et al. (2016).

derivative, which were combined with partial least square (PLS) regression for model calibration. Considering the complexity of pharmaceutical processes and real-time process data, novel pre-treatments, statistical regression approaches and their combinations should be additionally investigated. Published articles prove that NIR spectroscopy can predict film coating thickness, but they do not give clear answer to what is the upper limit of quantification. Korasa et al. (2016) observed higher prediction bias at approximately 40 μm, which could be a result of decreased sensitivity to thickness changes. On the other hand, Römer et al. (2008) detected spectral signal changes at coating thickness up to 300 μm. Upper limit of quantification depends on multiple factors, such as apparatus specifications, measurement settings, and coating properties, which should be object of future research. Finally, NIR spectroscopy was applied to study surface roughness and gloss of materials used in graphic arts (Larena et al., 2002) and in printing technology (Silfsten et al., 2012). In addition, it was shown that gloss strongly affects coating weight prediction of printed layers with the NIR (Mirschel et al., 2012). However, there is lack of similar studies in pharmaceutical technology, suggesting that study of gloss and roughness of pharmaceutical film coatings is another scientific area which deserves further attention in future.

3. Raman spectroscopy

Raman scattering, named after its discoverer Sir C. V. Raman, was firstly described in 1928 (Raman and Krishnan, 1928). Two years later Sir Raman was awarded a Nobel Prize in physics (The Royal Swedish Academy). The Raman effect is known as the inelastic energy exchange between the radiation and molecular vibrations. In Raman spectroscopy, samples are irradiated by monochromatic laser light in the visible or NIR wavelength region. Most of the incident light is scattered back at the same wavelength (Rayleigh scattering). However, very small fraction (i.e., approximately 10^{-8}) of light is scattered inelastically, resulting in slightly longer (Stokes scattering) or shorter (anti-Stokes scattering) wavelength of the scattered light (Fig. 3). The change in wavelength indicates that energy exchange between the incident light and the sample has occurred and this energy/wavelength change presents a basis for Raman spectroscopy measurement. The basic condition for the Raman scattering occurrence is a change in the electronic polarizability of the molecule, meaning that large polarizability changes lead to strong Raman scattering (Strachan et al., 2007; De Beer et al., 2011). The polarizability is defined as the ease with which the electron cloud is distorted. Consequently, Raman scattering

Table 2
Studies investigating applicability of Raman spectroscopy in monitoring of film coating unit operations for manufacturing of solid oral dosage forms.

Dosage form	Attribute	Process	Measurement	Reference
Tablets	Weight gain	Pan coating	In-line	El Hagrasy et al., 2006 Müller et al., 2010a
	Active ingredient content	Pan coating	Off-line In-line	Wirges et al., 2011 Müller et al., 2010a Müller et al., 2010b Wirges et al., 2013a Wirges et al., 2013b
	Coating thickness	Pan coating	In-line	Müller et al., 2012
	Mean dissolution time	Pan coating	In-line	Müller et al., 2012
	Curing progression	Dynamic curing in pan coater	Off-line	Gendre et al., 2012 Gendre et al., 2013
		Static curing	Off-line	Gendre et al., 2013
Pellets	Coating thickness	Fluid-bed coating	Off-line	Sovany et al., 2009 Nikowitz et al., 2014
			In-line	Hisazumi and Kleinebudde, 2017
	Sprayed quantity	Fluid-bed coating	In-line	Bogomolov et al., 2010
	Moisture content	Fluid-bed coating	In-line	Bogomolov et al., 2010

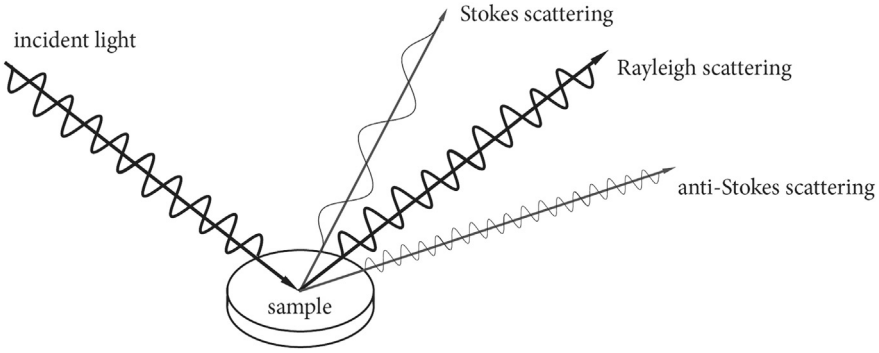

Fig. 3. In Raman spectroscopy, most of the incident light is scattered back at the same wavelength (Rayleigh scattering), while only small fraction of light is scattered at slightly longer (Stokes scattering) or shorter (anti-Stokes scattering) wavelengths.

is associated with delocalised electron systems in contrast to IR absorption, which is associated with polar molecules, hence IR and Raman spectroscopy can provide complementary information (Strachan et al., 2007).

As well as NIR spectroscopy, Raman spectroscopy is non-destructive, rapid approach, which can generate large volumes of real-time data directly in the process stream. Moreover, Raman spectroscopy can be even better at studying active pharmaceutical ingredients than the NIR, since most of active ingredients have aromatic or conjugated structures, which are strong Raman scatterers (Strachan et al., 2007). As written in the section above, NIR measurements can be strongly affected by the presence of water, which on the other hand is a very poor Raman scatterer, making this approach less susceptible to water content fluctuations. These properties are the main reason that Raman spectroscopy is becoming a very attractive PAT approach, which is confirmed by increasing number of scientific publications in the field. On the other hand, Raman spectroscopy also has its drawbacks. As mentioned above, most of the incident light is scattered at the same frequency and only very small proportion is scattered inelastically. Rayleigh scattering can be removed by interference filters or spectrometers; however, this does not solve the problem of poor Raman scattering intensity. One of the solutions for intensifying the signal could be increased energy of the incident light, i.e. higher laser intensity or lower laser wavelength, but both measures can also lead to more pronounced sample heating or even material decomposition. In addition, lower wavelength laser can induce fluorescence phenomenon, which can cause Raman signal masking (Johansson et al., 2002; Strachan et al., 2007; De Beer et al., 2011). Major breakthroughs in Raman process analysers have been made recently to overcome the latter difficulties; however, there is space for further improvements. As in the case of NIR spectroscopy, Raman spectra must be calibrated with the reference method prior to process monitoring. Spectral data pre-treatment methods and model construction approaches are similar to the NIR. Research articles studying applicability of Raman spectroscopy in film coating of solid oral dosage forms are discussed below and summarized in Table 2.

Applicability of in-line Raman spectroscopy in coating process was firstly demonstrated by El Hagrasy et al. (2006), who introduced the possibility of real-time monitoring of tablet coating using quantitative model calibrated with off-line weight gain measurements. Although univariate model was used in the study, it represented important milestone for later investigations. Following studies were focused on in-line Raman spectroscopy feasibility in active coating of tablets. Müller et al. (2010a) determined diprophylline content in real time during the coating of placebo tablets. In addition, the authors demonstrated the possibility of active ingredient content determination when tablet cores containing diprophylline were further coated with the same active ingredient. PLS model used in the study was calibrated with off-line UV measurements. In their next study, Müller et al. (2010b) validated the Raman procedure for in-line diprophylline content determination in agreement with the ICH guideline Q2. Feasibility of Raman spectroscopy as PAT tool in active coating of tablets was further investigated by Wirges et al. (2011), who used the model calibrated on mini scale to predict active ingredient content during the pan coating on micro scale, and hence showed that Raman spectroscopy can be implemented on different scales. The model was based on off-line Raman measurements. Again, diprophylline was used as the model active ingredient. Wirges and co-workers continued their research by investigating applicability of in-line Raman spectroscopy in monitoring and control of bi-layer tablets coating process with candesartan cilexetil containing suspension (Wirges et al., 2013a; Wirges et al., 2013b). Firstly, it was shown that real-time monitoring of active ingredient content can be successfully implemented in a lab scale drum coater and that in-line Raman spectroscopy can also handle complex dosage forms such as bi-layer tablets (Wirges et al., 2013a). The model, constructed at lab scale, was later transferred to production scale where process endpoint was successfully determined (Wirges et al., 2013b). In addition, the method was validated in accordance to European Medicine Agency's guideline. Müller et al. (2012) proved that in-line Raman spectroscopy can also be applied for the evaluation of other critical quality attributes besides active ingredient content when they successfully predicted mean dissolution time and coating thickness of sustained release coated tablets. The more detailed review of the studies investigating applicability of in-line Raman spectroscopy in tablet coating together with some interesting off-line Raman spectroscopy studies can be found in Knop and Kleinebudde (2013).

The number of studies investigating applicability of in-line Raman technology in pellet coating process is rather small. It was shown by Bogomolov et al. (2010) that Raman spectroscopy correlated well with coating spray quantity and in individual cases also with loss on drying measurements. The results of NIR and Raman spectral data augmentation presented in the article are rather surprising, since augmentation improved the quality of the PLS regression models for pellet moisture content determination, although Raman spectroscopy is poor water scatterer. On other hand, NIR and Raman data augmentation showed no significant beneficial effect in case of spray quantity PLS models. In this case, NIR spectral data most frequently resulted in the highest correlation. Such results are very interesting and do not show straightforward relation with the theoretical background of both spectroscopic approaches; thus, complementarity and comparability of NIR and Raman spectroscopy deserve further scientific attention. Suitability of Raman spectroscopy for coating thickness estimation of coated pellets is also described in the literature. Sovany et al. (2009) and Nikowitz et al. (2014) applied Raman spectroscopy to determine polymer coating thickness and showed that spectral measurements can provide accurate thickness determination of multi-particulate systems. However, the measurements were not taken in-line. In-line Raman monitoring of film-coating thickness on pellets was performed in a very recent study (Hisazumi and Kleinebudde, 2017), in which the authors successfully predicted film thicknesses of multi-layered pellets. In addition, MCR (multiple curve resolution) calibration showed better performance than most frequently applied PLS regression. To the best of our knowledge,

this is the only research article studying applicability of in-line Raman spectroscopy for coating thickness determination of film-coated pellets, suggesting that additional studies are needed to further investigate its usability for in-line evaluation of pellet coating process.

Mechanism of dynamic curing (Gendre et al., 2012) and comparison of static versus dynamic curing (Gendre et al., 2013) of ethylcelllulose coated tablets was characterised using Raman spectroscopy. The authors observed decrease of the peak at 1080 cm^{-1} as curing proceeded. The results were attributed to the rearrangement of polymer chains, leading to a densification and better organization of the coating layer. The measurements were taken off-line; however, the results suggest that real-time and in-line Raman measurements could also be performed. Further investigation is needed in this scientific field to clarify the feasibility of in-line measurements during the curing process and to evaluate possibility to predict drug release rate using Raman spectroscopy in real time.

The above review shows that Raman spectroscopy is a feasible PAT tool for evaluation of coating process, which can be scaled up to production environment and validated in accordance with the relevant guidelines. However, there are still a lot of un-investigated fields that need additional clarification. Firstly, usability of Raman spectroscopy for in-line monitoring of other critical quality attributes besides active ingredient content should be investigated, e.g. dissolution rate or gastro-resistance. In addition, applicability on new, less investigated model active ingredients should be clarified. There is also a lack of studies investigating the applicability of Raman spectroscopy in the evaluation of pellet coating process. Possibility of real-time monitoring of curing process and curing related characteristics (e.g., dissolution rate or physical-mechanical film properties) also deserves further scientific attention. The study of Bogomolov et al. (2010) showed that research findings are not always straightforward and that complementarity of Raman and NIR spectroscopy has to be further clarified. Unlike Bogomolov et al. (2010), who showed that NIR spectroscopy resulted in better PLS models for sprayed quantity than Raman spectroscopy, Cahyadi et al. (2010) found that Raman spectroscopy was more effective at differentiating coating thickness of tablets coated under different process conditions. Such findings suggest that comparison of both PAT approaches under similar process conditions and their pros and cons should be studied further. Finally, investigation of practical aspects, such as location of the probe or illumination angle (Kim et al., 2016), could lead to interesting conclusions and more efficient Raman tools handling.

4. Terahertz pulsed imaging

Terahertz electromagnetic radiation covers spectral range from 3.3 to 130 cm^{-1} (0.1–4 THz), which means that it spans in the range between mid-infrared (IR) and microwave radiation. Thus, terahertz region can also be named far-infrared radiation. In contrast to the IR region, which is related to intra-molecular vibrations, terahertz region is dominated by inter-molecular vibrations, corresponding to coherent, delocalized movements of large number of atoms and molecules. Therefore, terahertz spectroscopy (TPS) presents an excellent tool for characterisation of crystalline properties of pharmaceutical solids. TPS can be used in a wide range of pharmaceutical applications, such as analysis of crystal structures and their characterisation, active ingredient and polymorph quantification, and detection of phase transitions in solid samples (Shen, 2011; Haaser et al., 2013a). In contrast to crystalline materials, most of pharmaceutical excipients present in film coatings are amorphous. Thus, terahertz pulse can penetrate through them, allowing application of terahertz pulsed imaging (TPI) in film coating evaluation. In TPI, sample is irradiated with an ultrashort terahertz pulse. When incident pulse reaches the surface of an analyte, a fraction of the pulse is reflected to the detector at the air-coating interface and every subsequent interface due to the change in refractive index (Fig. 4). The layer/coating thickness (d) can be calculated from the measured signals using the equation below:

$$d = \frac{\Delta tc}{2n}$$

where Δt stands for the time difference between the pulse reflection at the coating-core interface and air-coating interface, c stands for the speed of light and n for refractive index of the material, which can be obtained using TPS (Russe et al., 2012; Haaser et al., 2013a). TPI measurement can be taken at one point of the investigated area (acquisition time of several milliseconds) or at several different spots. In case full scan measurement is carried out to map the whole surface of the tablet, it can take up to 60 min (May et al., 2011).

TPI is fast, non-ionizing, and non-destructive technique, which allows direct coating thickness measurement. In contrast to NIR and

Table 3
Studies investigating applicability of TPI, SFV, and image analysis in monitoring of film coating unit operations for manufacturing of solid oral dosage forms.

Method	Dosage form	Process	Measurement	Attribute	Reference
Terahertz pulsed imaging	Tablets	Pan coating	Off-line	Coating thickness Inter-tablet coating uniformity Intra-tablet coating uniformity	Maurer and Leuenberger, 2009
				Drug release	Ho et al., 2009
			In-line	Coating thickness	May et al., 2011
				Inter-tablet coating uniformity	Lin et al., 2015 Lin et al., 2017
Spatial filtering velocimetry	Pellets	Fluid bed coating	In-line	Particle size distribution	Folttmann et al., 2014 Hudovornik et al., 2015 Wiegel et al., 2016
				Coating thickness	Hudovornik et al., 2015
				Agglomeration	Wiegel et al., 2016
Image analysis	Pellets	NA	Off-line	Coating thickness	Larsen et al., 2003
		Rotor layering	Off-line	Particle size distribution Coating thickness	Heinicke and Schwartz, 2004
		Fluid-bed coating	Off-line	Particle size distribution	Heinicke and Schwartz, 2004
				Coating thickness	Možina et al., 2010
			Off-line	Agglomeration	Možina et al., 2010
			In-line	Coating thickness Inter-pellet coating uniformity Particle size distribution	Oman Kadunc et al., 2014
	Tablets	Pan coating	In-line	Appearance Weight gain Coating uniformity	García-Muñoz and Gierer, 2010

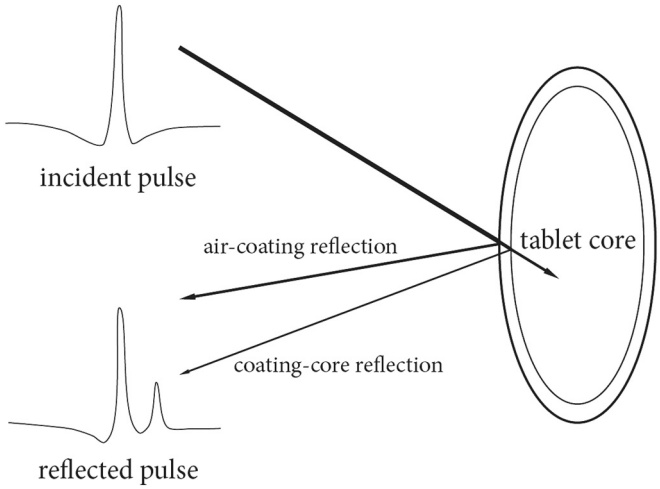

Fig. 4. The incident terahertz pulse is reflected at the air-coating interface and every subsequent interface due to the change in refractive index. Coating thickness can be calculated from the time delay between the surface reflection and the coating-core interface reflection.

Raman spectroscopy, no complex calibration of chemometric models is needed prior to the analysis. In addition, terahertz signal is strong enough to detect interfaces located up to 3 mm below the tablet surface (Zeitler et al., 2007) and can provide information from below the sample's surface (Ho et al., 2007). These benefits of TPI are the main reason that it has become widely recognized analytical technique in evaluation of film coated dosage forms and is becoming a promising tool in monitoring and control of film coating process.

There are several studies investigating the applicability of off-line and at-line TPI in the evaluation of different coating related characteristics. Proof-of-principle study was carried by Fitzgerald et al. (2005). In their study, TPI was capable to determine coating thickness of ibuprofen tablets coated with single or multiple layers. The waveforms, which were obtained in less than 20 ms, also allowed detection of individual layers in case of multiple-layer coated tablets. Zeitler et al. (2007) evaluated 3D TPI for non-destructive characterisation of different solid dosage forms, such as coated tablets, multi-layered controlled release tablets, and soft gelatine capsules. Authors determined the spatial and statistical distribution of coating thickness in single- and multi-layered tablets, the thickness of the gelatine capsule and managed to characterise the seal between the gelatine layers. The study proved that full scan mode produces large volumes of data, however measuring times are significantly extended (up to 50 min for a measurement). Some later researches extended the applicability of the TPI far beyond coating thickness determination. Ho et al. (2010) showed, using the TPI, that tablet central band exhibited thinnest film coating, highest surface roughness, and lowest coating density, and was thus identified as tablet's weak spot. The authors confirmed the latter statement with faster drug release from the central band. Terahertz radiation can penetrate deep into a sample, providing information about buried coating structures. Malaterre et al. (2010) detected internal coating alteration of the push-pull osmotic system's membrane with the TPI. The alteration appeared due to coating process interruption and led to significant decrease of drug release profiles. TPI can also be used for dissolution rate prediction, which can be done by straightforward correlation of coating thickness with mean dissolution time (Spencer et al., 2008) or, more interestingly, by building a PLS model between the terahertz waveform and mean dissolution time (MDT) (Ho et al., 2009). Ho et al. (2009) predicted MDT of cured tablets with different amount of applied polymer, showing that TPI can be useful technique for understanding and monitoring of coating unit operation. The above listed studies show that TPI is a valuable tool in tablet coating operations. On the other hand, there is a lack of studies investigating its applicability in evaluation of standard sized pellets (i.e., 0.5 mm to 2 mm). Haaser et al. (2013b) showed that it is possible to analyse drug layer and film coating layer thickness of pellets with the manual TPI setup (incident beam was manually focused on the highest point of the pellet surface and moved gradually over the entire investigated area), however additional studies are needed in the field. More information about the TPI in coating operations can be found in comprehensive review article by Haaser et al. (2013a).

Despite the numerous studies investigating the applicability of off-line and at-line TPI, process monitoring with the in-line TPI remains poorly investigated. Although at-line and off-line instruments enable fast and non-destructive monitoring of the coating process (Maurer and Leuenberger, 2009), in-line measurement still provides most valuable information within the shortest time and is thus the most representative PAT approach. The first study measuring coating thickness of randomly moving tablets in a production-scale pan coater with the in-line sensor was conducted by May et al. (2011). The authors mounted the sensor on the perforated coating pan and managed to measure up to 100 individual tablets per minute in real-time through the coating pan perforations. The in-line TPI provided measurements of sub-micron resolution, which were in good agreement with both off-line TPI and weight gain measurements. The biggest drawback of this proof-of-principle study was the inability of the sensor to determine film thickness below 40 μm. In another study (Lin et al., 2015), in-line TPI was used to determine film coating thickness and its inter-tablet variability during the coating process under different process conditions. The authors were capable to detect differences in coating thickness distributions due to process variations, such as removing of mixing baffles, addition of uncoated tablets, halting the drum, blockage of spray guns, and spray rate changes. In their next study, Lin et al. (2017) measured coating thickness and inter-tablet coating uniformity by in-line TPI combined with another cross-sectional imaging technique – OCT. The study showed promising results for evaluation of tablet film coating with a combination of two or more complementary in-line measuring approaches (please refer to Section 6.1 Optical coherence tomography for further details about this study). Above described in-line researches show high potential of in-line TPI in coating process monitoring, however additional effort is needed to improve method's lower quantification limit and to develop robust commercially available in-line TPI process analysers for routine process monitoring. In addition, advancement in TPI technology for automatic analysis of small dosage forms, such as coated pellets, is also desired. When these drawbacks are overcome, TPI can become even more applicable and recognized process analyser.

5. Particle size analysis

Techniques for in-process particle size determination are especially applicable in case of smaller dosage forms such as pellets, since coating thickness can be calculated simply from particle size increase information. In addition, particle sizing approaches are capable of detecting the initiation of agglomeration, an undesired phenomenon during coating process, which cannot be measured directly in real-time with other hereinabove described process analysers. Most recognized in-line particle sizing approaches can be divided into two groups, i.e. methods for chord length distribution (CLD) measuring and image analysis devices. There are also other approaches for in-process evaluation of particle size, such as on-line laser diffraction (Looser et al., 2010), however two groups of analysers described below are currently most frequently used in pharmaceutical manufacturing.

5.1. Chord length distribution (CLD) analysers

CLD analysers measure the length of the signal generated by the interaction between the laser beam and the analysed particle. In such

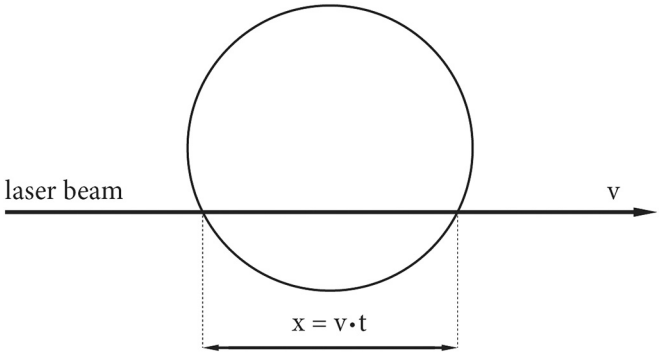

Fig. 5. CLD analysers calculate particle's chord length (x) from information about particle's (SFV) or laser's (FBRM) velocity (v) and time of the interaction between the laser beam and the analyte (t).

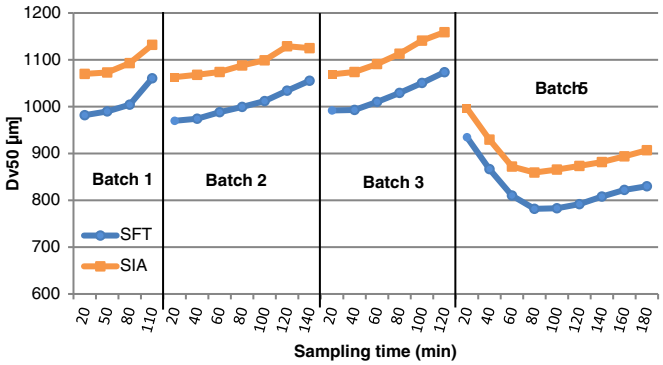

Fig. 6. Comparison of D_{v50} (median of volume distribution), measured by the in-line SFT (spatial filtering technique) and by off-line SIA (static image analysis), showed good correlation between both measuring approaches. The correlation was confirmed with the production of four batches of prolonged release coated pellets. This figure is taken from Hudovornik et al. (2015).

case, length of the signal presents particle's chord length (Fig. 5), which can be defined as a geometric line segment whose endpoints both lie on the surface of the particle (Silva et al., 2013). There are two well recognized CLD approaches mentioned in the literature, namely spatial filtering velocimetry (SFV) and focused beam reflectance measurement (FBRM). SFV can convert light obscuration signals from individual measured particles into particle size information. The measurement is made by a fibre optic array. Firstly, particle's velocity (v) is calculated from the impulses, which are produced when particle passes a series of photodetectors. When particle's velocity (v) is known, its chord length (x) can be determined from the duration of a signal on one additional optical fibre (t) using the below equation:

$$x = v \cdot t - d$$

where d stands for the diameter of the optical fibre (Schmidt-Lehr et al., 2007; Silva et al., 2013). Chord length can be any line of the intersection of the 2D projection of the particle, since the flight path of the analysed particle is random (Schmidt-Lehr et al., 2007). SFV probe is suitable for size measurements in the range 50–6000 µm with an uncertainty of 1% and for velocity measurements between 0.01 m/s and 50 m/s with an uncertainty of 0.5%, which makes this PAT analyser a very applicable tool in several technological processes, such as fluid-bed granulation, high shear wet granulation, Wurster coating, spray drying, and milling (Petrak et al., 2011; Loh et al., 2015). Additional information about SFV technique and its application can be found in the literature (Petrak and Rauh, 2006; (Schmidt-Lehr et al., 2007; Petrak et al., 2011; Silva et al., 2013).

Recent studies show that the SFV probe is becoming a valuable tool in the monitoring of pellet coating process. Folttmann et al. (2014) used the SFV to monitor the increase of pellet size during the Wurster coating process in-line. The measurements were consistent with the reference at-line digital image analysis (DIA). In addition, it was shown that applied film thickness can be calculated from the real-time particle size measurements. Hudovornik et al. (2015) showed that in-line SFV measurements correlated with more conventional off-line particle size measurements (sieve analysis, static image analysis) and were consistent with coating dispersion spray rate changes (Fig. 6). Moreover, it was shown in the study that SFV was capable to detect and quantify attrition of the pellets. However, SFV failed to adequately measure agglomeration phenomenon. In contrast, it was suggested in another recently published study (Wiegel et al., 2016) that agglomerates can be detected, in case that pellets are over-wetted, by the increase of the $x_{90,3}$ (ninetieth percentile of volume distribution). The above studies show that SFV is an applicable analyser in pellet coating operations; however, additional studies are needed to clarify its ability to evaluate particle agglomeration.

Measuring principle of FBRM is somewhat different from SFV. FBRM probe creates a laser beam which rotates at a high speed (i.e., 2–8 m/s). When tightly-focused laser beam hits a particle, the light is reflected and propagated back to the probe where the duration of the backscattered light is measured. The chord length can then be calculated by multiplying the length of the measured signal with the laser beam scan speed (Silva et al., 2013). FBRM is capable to measure particles with chord length up to 3000 µm (Huang et al., 2010) and can thus be used for monitoring of several different processes. Silva et al. (2013) showed that particle size determination of pellets having different diameters (i.e., Cellets® 350, Cellets® 500, and Cellets® 1000) suspended in Miglyol® 812 was possible with the FBRM. Size parameters determined by the FBRM were different from the reference methods (laser diffraction, sieve analysis) due to different measuring principle; however, results were consistent with the size related properties of the sample. Kukec et al. (2013) compared in-line FBRM and SFV measurements during the in situ fluid bed melt granulation. In the study, FBRM probe was successfully employed to monitor the effect of critical process and formulation parameters on growth kinetics. In addition, FBRM and SFV probes showed similar particle growth trends. Particle size (volume-based median) up to 750 µm was determined by the FBRM in the study. The above studies show that FBRM probe is a useful in-process analysing tool that is capable to measure particle size in the range of regular sized pellets. However, additional research is needed to confirm applicability of the FBRM in real-time monitoring of pellet coating processes.

5.2. Image analysis

Image analysis systems determine particle shape and size parameters based on the image taken with a digital camera. Such analysers consist of a hardware system for image acquisition and a software system for image segmentation and calculation of the particle size and shape parameters. System for image acquisition consists of three key elements: digital camera, light source, and lens. Digital camera must be capable of rapid image acquisition and adequate image quality of moving particles. Two types of digital cameras are most commonly used in the existing image analysers, namely CCD (charge-coupled device) and CMOS (complementary metal-oxide semiconductor) image sensors. LED (light-emitting diode) is primarily used light source, since it enables sufficient luminous intensities, which is essential for rapid image acquisition, and does not overheat extensively with time. Telephoto lens is commonly used lens in visual imaging systems. Basic principle of particle size determination is common for different image analysis systems mentioned in the literature. However, systems differ in both image acquisition and image processing specifics (Närvänen et al., 2008; Sandler, 2011; Treffer et al., 2014; Oman Kadunc et al., 2014).

Image analysis for coating thickness determination was firstly applied in the static environment. Kennedy and Niebergall (1997)

determined coating thickness and coating uniformity of hot-melt coated spheres with a red dye incorporated into the polyethylene glycol and Larsen et al. (2003) estimated mean pellet size and coating thickness of coated sugar spheres with an accuracy of ± 1.2 μm. Heinicke and Schwartz (2004) made a comprehensive evaluation of dynamic image analysis for measuring particle size distribution of inert spheres, drug-layered pellets, and polymer-coated pellets in the size range from 425 μm to 1400 μm. Coating thickness differences between samples differing by 2% coat weight (equal to 4 μm thickness) were detected and more than 15,000 particles could be measured in less than 5 min. Study showed that moving pellets can be efficiently measured with the image analysis. A step further to real-time monitoring of the pellet coating process was made by Možina et al. (2010). The authors measured the size and shape characteristics of fluid-bed coated pellets with the digital visual imaging system equipped with a vibrating surface, which ensured constant and continuous flow of the pellets from the dosing unit into the measuring area. Measured pellets were classified in different classes according to their circularity and coating thickness estimation was calculated from the class of the most spherical pellets. Estimated coating thickness of nine consecutive samples in the coating thickness range 0–35 μm was consistent with the process flow. It was suggested in the article that method could be used as a tool for understanding, designing, and optimizing of coating processes according to the PAT guidance. Silva et al. (2013) studied the applicability of two image-based particle sizing technologies for in-process control, i.e. the photometric stereo unit Flashsizer 3D® and The Eyecon® particle sizing technology. Both measuring approaches are described in detail in the article. The authors showed that both techniques can be used for size evaluation of granules and pellets. However, measurements were taken in off-line mode, which is not the optimal indicator of real-time robustness of the tested methods.

The applicability of the Eyecon® technology for in-line size measurement of pellets was investigated by Treffer et al. (2014). Although hot-melt extruded pellets were monitored in the study, the findings are also important for evaluating the applicability of the technique in in-process control of pellet coating operations. The method was found as a useful tool for determination of size and shape of the pellets produced by hot-melt extrusion. In addition, method provided information about surface texture. The biggest drawback of the method was its inability to correctly detect black, strongly reflecting or transparent materials. Oman Kadunc et al. (2014) measured particle size of pellets through the observation window of a laboratory Wurster coating apparatus. Coating thickness growth was determined in real-time and accuracy of the results was confirmed with the reference spectrophotometric determination (R^2 value of 0.998). In addition, inter-pellet coating uniformity was assessed through statistical analysis of the particle size distribution. Such results suggest that image analysis is an important approach for in-line and real-time monitoring of pellet coating process. Nevertheless, the number of studies investigating pellet coating process with image analysis is insufficient and additional work is needed to assess its robustness and performance. Future studies should evaluate the effect of critical material attributes, such as inert sphere characteristics, pellet size distribution, coating composition, and effect of critical process parameters, which could lead to pellet agglomeration or attrition phenomena, on the measured particle size parameters.

Although image analysis is particularly suitable for monitoring of pellet coating process, the study of García-Muñoz and Gierer (2010) proved that it is also applicable in film coating of tablets. The authors determined cosmetic end-point (the point when appearance of the tablet is no longer changing) of the film-coating step, calculated the coating level and coating distribution across tablets by using a simple webcam installed inside the coater in combination with multivariate data analysis. Such approach could provide a cost-effective tool to replace visual inspection. The study clearly illustrates that there are numerous possibilities of incorporating innovative PAT solutions in different fields of pharmaceutical technology.

6. Other process analysers

Four less recognized process analysers are reviewed in the following sections. Based on the published studies, below described process analytical approaches are promising tools, which could become valuable PAT analysers in the future. However, further research and improvement are needed to develop solutions for common application in pharmaceutical coating processes.

Optical coherence tomography (OCT) is becoming recognisable PAT analyser, which is confirmed by some recently published studies, investigating in-line measurement of solid oral dosage forms during the film coating step (see Section 6.1 below). However, studies were carried out with custom built solutions and thickness evaluation algorithms needs to be optimized before the arrival of commercially available in-line systems. Acoustic emission (AE) and microwave resonance technology (MRT) have not been used for monitoring of film coating process yet. However, it is evident from the existing studies (please refer to Sections 6.2 and 6.3 below) that both methods are capable to determine various physical characteristics of the evaluated material in fluidized bed machine in real time. Such results suggest that both analysers could become applicable tools for monitoring of coating process in fluid bed coater as well. Laser induced breakdown spectroscopy (LIBS) was classified into this section, since it enables rapid and direct measurement of film coating thickness and uniformity (please refer to Section 6.4). However, the number of studies investigating at-line LIBS measurements is rather small and its future applicability within the PAT framework could be limited due to the destructiveness of the method.

6.1. Optical coherence tomography

Optical coherence tomography (OCT) is a method based on low-coherence interferometry and employs light sources with high spatial but low temporal coherence, such as superluminescent diodes or femtosecond lasers with coherence lengths in the range of only several microns. Short coherence length acts as a temporal filter for photons that are back-reflected or back-scattered from the sample structures, such as interfaces, impurities, pores, and cells. The photons incoming from the sample interfere with the photons back-scattered from the reference mirror and cause a signal. The signal, however, is generated only if photons from the reference mirror and the sample surface arrive at the detector within short coherence time gate. Coherence length of low coherence light sources lies in the region of 1–15 μm enabling high axial (depth) resolution of this approach. OCT is used to generate cross-sectional depth-resolved two- or three-dimensional images of evaluated samples (Koller et al., 2011; Markl et al., 2014). It is non-destructive, contact-free, high-resolution approach, which enables acquisition of in-depth images in real time. Moreover, no chemometric calibration is required prior to measurements making the OCT promising process analyser within the PAT framework.

The studies show that OCT is capable of quantifying tablet coating with high axial resolution (0.9 μm) (Zhong et al., 2011), ranging from uncoated tablets to coating thicknesses up to 70 μm and can be used for the characterisation of tablet coatings sampled at different stages of a coating process due to high-speed of the measurement (Koller et al., 2011). Despite many advantages of the OCT, the method was not evaluated as an in-line process monitoring tool until recently. The feasibility of the OCT as an in-line quality control tool was firstly investigated by Markl et al. (2014). The authors used the spectral-domain OCT system with centre wavelength of 830 nm, which proved superior over 1325 nm system during the off-line evaluation. Experimental data was acquired by moving the OCT sensor head across a static tablet bed to imitate in-process measuring conditions. Examining of the coating homogeneity turned more difficult with increasing the transverse speed, but the coating thickness was still accurately determined at velocities up to 0.7 m/s. In their following study, Markl et al. (2015b) used the in-line OCT system to measure pellet coating thickness and

uniformity in a fluid-bed apparatus. Coating growth, intra-, and inter-pellet coating uniformity was possible with the in-line system. In addition, in-line OCT measurements were validated with off-line OCT and image analysis. However, coating thickness was calculated manually from the in-line OCT images, which is not a suitable approach for efficient in-process monitoring. A step further was made in the study of in-line monitoring of the pharmaceutical pan coating process (Markl et al., 2015a) where automated thickness evaluation algorithm was employed for the first time. The study presented a big step towards a real-time OCT measurement implementation, but the authors claim that several improvements and optimizations of the algorithm are needed in the future.

OCT has high axial and lateral resolution (0.9 μm and 20 μm, respectively) and is capable of quantifying film coatings as thin as 10 μm (Zhong et al., 2011; Lin et al., 2017). Its main drawback is relatively low upper quantification limit (60–70 μm) due to the strong scattering of the short wavelength OCT radiation. On the other hand, terahertz radiation has longer wavelength and is less prone to scattering. Thus, it is capable to quantify thicker coatings up to few hundreds microns (May et al., 2011; Zhong et al., 2011). However, TPI's achieved axial and lateral resolution are only 30–40 μm and 150–250 μm, respectively (Shen, 2011). Therefore, complementary use of OCT and TPI could present a powerful PAT combination for monitoring coating process over the wide thickness range, which was proved in the recent study by Lin et al. (2017). The authors measured film thickness of the individual tablets in a custom-built laboratory coating unit, using both TPI and OCT in-line measurements. The setup allowed monitoring of coating thickness in the range from 20 μm to greater than 250 μm. However, the study was conducted with custom-built hardware setup and in-line measurements were processed with algorithms which need further improvements, showing that there is still a lot of obstacles before commercially available systems for routine application will be available.

To sum up, OCT is a rapidly evolving measuring technique, which shows great potential for in-line evaluation of film coating process. Nevertheless, considerable scientific effort is needed to get beyond the proof-of-concept phase of this approach. Additional drawback is OCT's inability to measure thick coatings or detect structures deeper inside the tablets (Zhong et al., 2011). Recent studies (Zhong et al., 2011; Lin et al., 2017) show that this drawback can be overcome by complementary monitoring with other cross-sectional imaging techniques, such as TPI.

6.2. Acoustic emission

The basic concept of acoustic emission (AE) is to measure acoustic vibrations that are generated by particle-particle or particle-chamber collisions and frictions during the process. The shape of the measured acoustic signal depends on the physical properties of the moving particle (e.g., size, shape, hardness, density, porosity, moisture content, and uniformity of composition) and on its kinetic energy (Matero et al., 2009; Burggraeve et al., 2013). If particle characteristics change during the process, these changes affect the acoustic signal, which can be used for real-time evaluation of multiple process and product variables. Acoustic signals are measured in time domain and transformed to more useful format as frequency spectra to allow multivariate analysis of the measured data. Signal transformation consists of amplification to maximise digital resolution, analogue to digital (A/D) conversion, window transformation to avoid spectral leakage, and fast Fourier transformation (FFT) (Ihunegbo et al., 2013). The outcome of the acoustic measurement is a multivariate AE spectrum, which can be evaluated using well-known chemometric techniques such as PCA and PLS to obtain desired information. Acoustic signal is usually measured in the high frequency range (70–500 kHz) because this range can propagate through solid materials but attenuate rapidly in air (Burggraeve et al., 2013). To the best of our knowledge, there are no published studies investigating applicability of AE in coating of pharmaceutical dosage forms. However, the below studies show that method can be a valuable in-line tool for determination of several attributes that are relevant in coating processes.

One of the first AE process studies (Tsujimoto et al., 2000) investigated a high-frequency (140 kHz) sensor in monitoring fluidization of spherical particles in fluidized bed machine. It was shown that AE is capable of fluidization phenomenon monitoring, since direct correlation between AE amplitude and evaluated fluidization parameters (i.e., dimensionless excess gas velocity, dimensionless expanded bed height) was observed. Moreover, it was confirmed that mean AE amplitude could detect unstable fluidization caused by increased moisture content. Water content is another important critical attribute that can be determined by the AE. Ihunegbo et al. (2013) placed AE sensors onto the exterior wall of the fluidized bed and predicted water content in silica gel particles from acoustic spectra using the PLS regression. The values predicted by the most promising AE sensor were consistent with the reference method measurements (R^2 = 0.99) within very wide tested range (0–36% water). Several studies suggest that particle size also can be estimated by the AE. Matero et al. (2009) were able to extract granule size information from the AE spectra and in another study (Matero et al., 2010) the authors showed that AE data recorded in the nucleation phase of the granulation correlated with the final particle size distribution. Granule size distribution parameters (D(v,0.1), D(v,0.5), and D(v, 0.9)) were also successfully predicted from acoustic spectra using the PLS by Poutiainen et al. (2012). However, there is still a long way towards routine particle size determination with the AE in pharmaceutical industry, since authors themselves claim that more research is needed to get an insight into the granulation (Matero et al., 2009) and it can only be speculated whether the AE is a suitable option for accurate and precise particle size determination when various process conditions are applied (Poutiainen et al., 2012). All in all, AE could be a potential tool for monitoring of film coating process. However, extensive experimental input will be needed to evaluate its usability in the field.

6.3. Microwave resonance technology

Microwave resonance technology (MRT) is a novel approach for measuring material's physical properties, which is based on the interaction between the water molecules and electromagnetic field. The measuring frequency of the stray field MRT sensor is defined by the resonance wavelength of the microwave inducing resonator. In case the electrical field of a resonator is loaded with material, increasing storage of electric field results in reduction of resonance energy. During the measurement, the increasing water and material load in the monitored area leads to decreasing of the resonance frequency and simultaneously to magnification of the frequency band width (Fig. 7), enabling determination of density revised moisture measurement or moisture revised density measurement (Buschmüller et al., 2008; Lourenço et al., 2011). It was shown that physically bound water can be easily determined by calculating the ratio between the band width increase and decrease of the resonance frequency (Knöchel et al., 2007). The resonators used for the MRT monitoring respond with high sensibility; hence, high accuracy of measurements is possible (Buschmüller et al., 2008). More information about this novel approach can be found in the literature (Knöchel et al., 2007). Until now, no studies investigating MRT applicability in the pharmaceutical coating operations have been published, but below studies illustrate that MRT is a promising tool, which could generate useful data during the coating process in real time.

Buschmüller et al. (2008) developed in-line MRT sensor and used it for monitoring of placebo granules during the drying stage in two different fluid bed dryers. In-line MRT measurements were in good agreement with both reference off-line methods, i.e. loss on drying and Karl Fischer titration, in a wide range of moisture content (up to 20%).

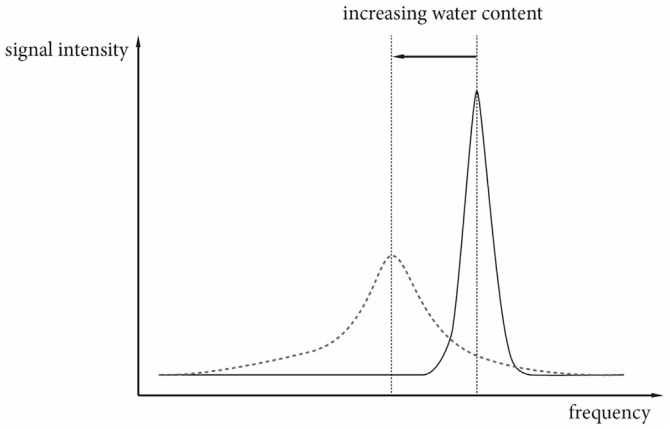

Fig. 7. The increase in water content and material load result in decrease of the microwave resonance frequency and in broadening of the frequency band width. Moisture content can be calculated from the ratio of band width magnification and decrease of resonance frequency.

In addition, the study suggested that the in-line measurements were not affected by the inlet air flow nor the material density in the fluidized bed. Recent study by Lourenço et al. (2011) showed even greater applicability of this novel in-line approach. 192 industrial granulation batches were monitored throughout the whole process (mixing, spraying, and drying) with the MRT. Besides moisture, density and temperature were also measured by the MRT. The multivariate data analysis of the MRT results showed that season of the year noticeably influenced the ongoing process and led to differences of final particle size distribution. In addition, the PLS model, which was capable to predict approximate final particle size distribution from the MRT determined process trajectories, was developed.

In the recent study, Nohlert et al. (2014) presented possibility of in-line measuring principle based on microwave resonance phenomena, which differs from the hereinabove presented stray field MRT. Stray field MRT is based on the local field of the resonator, while Nohlert et al. (2014) introduced the measurement in which process vessel is exploited as a microwave cavity resonator. Such approach enabled global monitoring of fluid bed process by measuring relative changes in complex resonance frequencies, which were related to permittivity distribution inside the process chamber. The principle was evaluated on coating of microcrystalline cellulose particles with a solution of mannitol and ethylene glycol vinyl acetate polymer. The authors observed growth in size during the coating process, showed material build-up on the cavity wall, and detected liquid spraying onto the particles. However, no exact values of the observed quality attributes were presented in this proof-of-principle study, showing that there is still a long way towards routine use of such measuring approach.

6.4. Laser induced breakdown spectroscopy

Although laser induced breakdown spectroscopy (LIBS) is a destructive measuring technique, it can represent a useful at-line PAT tool for rapid and direct determination of coating thickness and intra- and inter- tablet coating uniformity. In addition, LIBS is also a convenient tool for qualitative and quantitative elemental analysis of the monitored coating area. The method is based on atomic emission spectroscopy of laser-produced plasma. A laser pulse is focused onto the sample where it ablates the observed material and induces the plasma formation. In the plasma, ablated constituents are vaporized, dissociated into atomic species and brought to excited state. When atoms return to their ground state, they emit characteristic radiation, which is observed in the ultraviolet, visible, and near-infrared ranges. By resolving the emitted light, the constituents of the monitored area can be identified by characteristic lines/bands and quantified by the emission intensity. Coating thickness can be later determined by examining signal intensities as a function of the number of laser shots needed to penetrate the coating (Mowery et al., 2002; Madamba et al., 2007; Dubey et al., 2011).

LIBS was utilized for the first time for determining thickness and uniformity of pharmaceutical coating by Mowery et al. (2002), who observed decrease in emission's intensity of elements present in the enteric coating as a function of the number of laser pulses. Measured coating thickness was in good agreement with the SEM measurements. In addition, LIBS detected a change in coating thickness of less than 2.5% over a coating range from 5 to 21% by weight of 100 mg tablet. It was later shown that LIBS is not only capable to predict coating thickness and its uniformity but also coating's photoprotective potential as a function of coating thickness and concentration of ferric oxide in the coating (Madamba et al., 2007). The applicability of LIBS in pan coating monitoring was shown in the recent study (Dubey et al., 2011). LIBS correlated well with the weight gain measurements at different time intervals of the pan coating and was capable to detect tablet-to-tablet coating variability, which could be a consequence of inadequate mixing performance of the coating device.

7. Conclusion

Initiatives and programmes of medicine agencies have enhanced extensive research and development of new tools for efficient monitoring and control of pharmaceutical processes. NIR and Raman spectroscopy are the most widely used process analysers in film coating, although the number of alternative measuring approaches is increasing rapidly. The main advantage of spectroscopic methods is their ability to determine multiple critical process attributes simultaneously, which makes them “the ultimate PAT tools”. However, efficient spectroscopic monitoring requires development of multivariate models, for which significant time, material, and human resources are needed.

On the other hand, no complex chemometrics is needed for TPI, CLD measurement, and image analysis, since they can measure the critical attribute of interest directly. This is probably the reason that these methods are becoming widely used analysers in film coating processes. Their main drawback is narrower applicability, since they are generally designed to measure a single attribute, i.e. coating thickness/particle size.

Simultaneous application of multiple process analysers could be one of the solutions for comprehensive process monitoring and efficient control of all critical quality and performance attributes. In addition, when defining process monitoring strategy both process and analyser characteristics must be considered. Since number of process parameters and material attributes in film coating is very high, the universal process analyser does not exist. Therefore, new approaches, such as OCT, AE, MRT, and LIBS, are becoming important part of the PAT.

To sum up, there are a number of process analysers, which are capable of generating large volumes of applicable data during the film coating process of solid dosage forms. Efficient process monitoring in combination with other PAT tools can lead to comprehensive design, analysis, and control of complex coating processes. However, there are many drawbacks and limitations of the existing approaches, which require extensive research and development in the future.

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