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Review

Study progression in application of process analytical technologies on film coating

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ABSTRACT

Film coating is an important unit operation to produce solid dosage forms, thereby, the monitoring of this process is helpful to find problems in time and improve the quality of coated products. Traditional methods adopted to monitor this process include measurement of coating weight gain, performance of disintegration and dissolution test, etc. However, not only do these methods cause destruction to the samples, but also consume time and energy. There have recently emerged the applications of process analytical technologies (PAT) on film coating, especially some novel spectroscopic and imaging technologies, which have the potential to real-time track the progress in film coating and optimize production efficiency. This article gives an overview on the application of such technologies for film coating, with the goal to provide a reference for the further researches.

1. Introduction

In the field of industrial manufacturing, the implementation of real-time analysis of products, holds great significance for both the management and optimization of the whole production process, as well as the improvement in product quality. In the past few decades, the application of process analytical technologies (PAT) to monitor pharmaceutical unit operation has drawn more and more attention. PAT is the key element of the "21st century medicine current good manufacturing practices – based on risk" initiative, which is issued by FDA [1,2]. The primary goal of the implementation of PAT for film coating is "process understanding, optimization of manufacturing efficiency, improvement of product quality and reproducibility" [3]. More specifically, the application of PAT on film coating is reflected in these aspects: (1) measurement of average amount of coating and average coating thickness on tablets/pellets [4], (2) determination of coating uniformity and process endpoint [5], (3) provision of information on coating uniformity/variability within the inter- or

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intra-tablet [4], (4) plotting of coating structure [6]. Coated products are generally used as final products of the solid dosage forms, thereby their quality will more or less affect the specific performance of the active pharmaceutical ingredients (API). In most cases, a certain amount of coating thickness and uniformity is imperative to maintain the quality, stability and security of the solid dosage forms, which is associated with functionalities, including desired amount of drug released at the specific site, masking unpleasant taste or odor, improving esthetic appearance of a drug product, etc. Therefore the monitoring of these parameters during coating process is in urgent need. Traditional methods used to monitor these parameters are to collect limited samples from a coating pan or a fluidized bed at interval time, while the implementation of PAT can achieve the goal of real-time analysis of the coating process. PAT offer major advantages over the traditional methods in the acquirement of analytical data and the time used to monitor the coating process. Within the PAT framework, process data can be collected during the whole progress of a coated product and a considerably larger fraction of sample units could be analyzed during manufacturing, thus providing more insight into the process and greater confidence in the quality of the final product [3].

The performed measurements by process analysis can be classified into four types [7]: in-line, no removal of the sample; on-line, sample is diverted from the main process, analyzed and may be returned; at-line, sample is removed and analyzed closed to the process; off-line, sample is removed and analyzed away from the process. Compared to at-line methods, result obtained by in-line or on-line measurements should be markedly faster. It is hard to define the difference between at-line and off-line measurement in lab scale processing, because coating equipment and analytical procedure often take place in the same lab.

PAT can avoid the disadvantages of traditional coating monitoring methods, such as measurement of coating weight gain (gravimetric method), though it is a rapid and currently the most widely used evaluation methods [8], it does not provide information regarding the coating material and coating uniformity, and neglect the ruptures of core material and the accuracy of the results due to the different mass loss within the samples during drying/curing process [1]. However, the disintegration time limit or *in vitro* dissolution method, dose not only cause destruction to the samples, but furthermore consume time and energy [9]. Additionally, PAT can be used for real-time monitoring and acquisition of data information from a large amount of samples through the entire coating progress, which is helpful to fully understand the coating process and provide more reliance on the quality of the final product [3]. Thus, it is speculated that there is a great potential in the application of PAT on film coating according to the principles of quality by design (QbD). The currently reported techniques used as PAT to monitor the coating process include: (1) spectroscopic techniques, such as near infrared spectrum (NIRS) [8,10], Raman spectroscopy [3,11], laser induced breakdown spectroscopy (LIBS) [12–14]; (2) imaging techniques, such as terahertz pulse imaging (TPI) [15,16], near infrared imaging [1], magnetic resonance imaging (MRI) [17]; (3) microscopic techniques, such as confocal laser scanning microscope (CLSM) [6], atomic force microscope (AFM) [6], scanning electron microscope (SEM) [1,6], etc. Since the microscopic techniques tend to destroy samples, they are not suitable for online analysis and the present studies focus more on spectroscopic and imaging techniques. This article mainly discussed the development of these two techniques for film coating.

2. Access to establish process analytical technologies (PAT)

The implementing process analyzers into coating process streams can be realized mainly through the following steps (Fig. 1). For the coating of tablets, it is commonly performed in a pan coater, while for the coating of pellets, it is generally done in a fluidized bed to reduce adhesion of the particles during coating. To successfully and accurately monitor the coating process, some aspects should be considered [18]. First, a suitable process analyzer or combination of complementary process analyzers should be selected according to the attributes of the measured samples to monitor the desired critical process and product information. Then, it is necessary to determine the locations in the process streams where and how process analyzers should be and can be implemented to monitor the required information, as the location of the process analyzer in the equipment is a critical factor. Here, a NIR probe is taken as an example [19]. In drum coaters it is usually mounted above the moving tablet bed in a position where no spray liquid can hit the measuring window. When an immersion probe is used fouling can be prevented by purging the

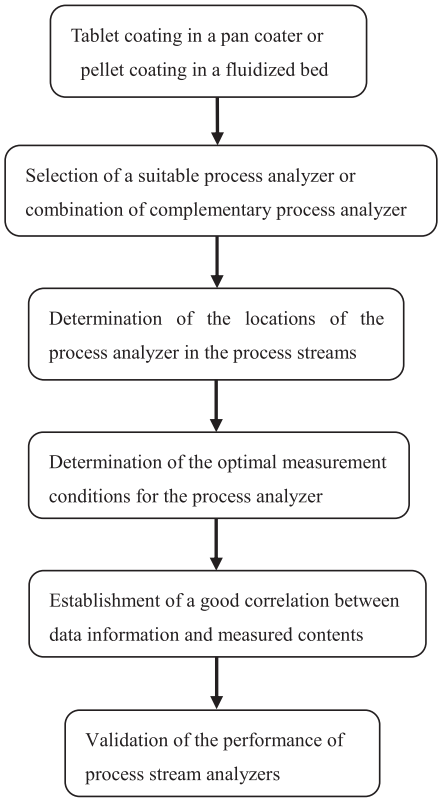

Fig. 1 – Major steps to establish process analytical technologies.

probe with gas. In fluidized bed equipment the probe can be integrated in the cylinder wall. Fouling seems to be a minor problem in this case. Afterward, the optimal measurement conditions for the process analyzer should be determined to obtain useful data and establish a good correlation between data information and measured contents, such as average weight gain of the product or the amount of coated ingredient at each time interval [9,11], coating thickness [20], or coating times [21,60]. Since film coating is a multivariate unit operation with various process parameters, i.e. spray rate, inlet- and exhaust air temperature, inlet- and exhaust air flow, atomization air pressure, pan speed and gun to bed distance [4], it is not an easy task to model and predict the characteristics of the coated products. To minimize the influence of processing variables, some mechanistic or physical models are often invoked for quantitative calibration and explanation of correlation between spectroscopic variables and response variables [20,57], such as principal component analysis (PCA) [4], partial least squares (PLS) [11,20], net analyte signal (NAS) [21], classical least squares (CLS) [20], target factor analysis (TFA) [20], discrete element method (DEM) [21], etc. Finally, validation of the performance of process stream analyzers is performed in designed batches.

3. Spectroscopic techniques

3.1. *Near infrared spectroscopy (NIRS)*

According to ASTM, near-infrared light is referred to as the electromagnetic wave whose wavelength falls between visible light and infrared region, namely, the wavelength in the range of 780–526 nm (Fig. 2). A majority of substances in nature are abundant in absorption peak or emission peak in this wavelength range. The quantitative or qualitative analysis of these substances can be carried out by NIRS depending on the characteristic absorption peak intensity of the measured substances. NIRS is regarded as one of the most widely used and promising PAT. The interest in NIRS lies in its advantages over alternative instrumental techniques: (1) it can be used for qualitative evaluation of the samples by clustering principle, and quantitative assessment of the samples by multivariate calibration method and the established quantitative model based on the known properties or constitutes of the samples; (2) it is a rapid analytical tool with high output, and suitable for analysis of multiple complex components; (3) it requires minimal or no sample preparation with low cost analysis [22]; (4) it does not destroy samples, consume reagent and pollute the environment, which makes it a "green analytical technology" [23]; (5) there is no demand for the physical status of the samples, whether they are in the status of gas, liquid or solid, qualitative/quantitative analysis is available; (6) the introduction of optical fiber enables the usage of NIRS extended to process analysis and remote analysis, concomitantly makes the design of spectrometer more miniaturization.

In the art of pharmaceutical coating, the performance of NIRS is mainly to quantify the coating process [11,24], such as determination of the coating thickness and coating end point, analysis of coating uniformity or variations. Table 1 shows the examples of monitoring of the coating process by NIRS. As shown in Table 1, NIRS has been applied off-line, at-line, and in-line in a fluidized bed apparatus and in a pan coater. And the currently performed researches on the monitoring of coating process are primarily for tablets rather than pellets. Most of these researches on pellets were focused on establishing proper methodology, which was applied to analyze coating thickness or coating thickness concerning drug-release behavior. But Min JL and coworkers has pointed out that the combination of NIRS and laser diffraction particle size analyzer or confocal laser scanning microscopy can be used to accurately measure the coating thickness of the pellets based on partial least squares calibration model [32]. NIR spectra were collected in real-time during the coating process via a fiber-optic diffuse reflectance probe that was connected to the fluid-bed coater, as shown in Fig. 3. The major problem associated with measurement of pellet coating thickness by NIRS is poor correlation due to the differences in spectral information from dynamic fluidized bed after statistical treatment [32]. However, for the coating of tablets, the uneven distribution of tablets in a pan coater during coating process

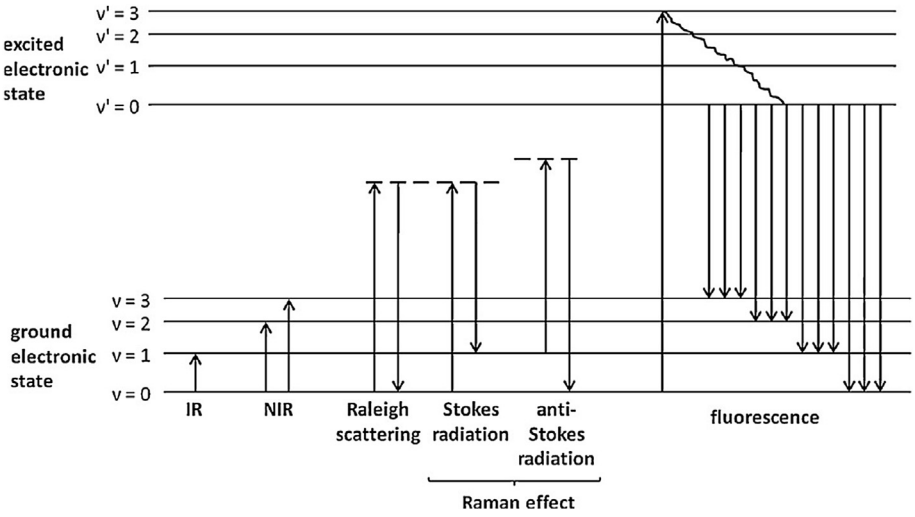

Fig. 2 – IR and NIR absorption, the Raman effect and fluorescence (reproduced from Beer et al. [18]).

Table 1 – Applications of NIRS in the field of pharmaceutical coating.

Author	Year	Core	Measurement	Calculation model	Applications	Ref.
Buchanan et al.	1996 (first introduced)	Tablet	Off-line	PLS	To establish a correlation between the amount of API in the active coating measured by HPLC and predicted from NIR spectra.	[25]
Andersson et al.	1999	Tablet	At-line	PLS	To investigate the coating of two layer tablets with different APIs in each layer.	[26]
Perez-Ramos et al.	2005 (first introduced)	Tablet	In-line	Univariate	To analyze tablet film coating thickness in a lab scale pan coater.	[27]
Römer et al.	2008	Tablet	In-line	Multivariate	To measure coating thickness in a lab scale pan coater.	[28]
Gendre et al.	2011	Tablet	In-line	PLS	To correlate NIR spectra with weigh gain and TPI measurements.	[29]
Andersson et al.	2000 (first introduced)	Pellet	In-line	PLS	To predict coating thickness with several data pretreatment methods.	[30]
Bogomolov et al.	2010	Pellet	In-line	PLS	To monitor the coating process of pellets in fluid bed apparatuses and to predict the end point of a coating operation.	[31]

may make changes in the sensitivity of the sensor, potentially leading to inaccurate analytical results [11]. Lee and coworkers demonstrated that the average method could successfully circumvent the problems existing in the NIRS analytical technology and was the best way to predict coating thickness [33].

3.2. *Raman spectroscopy*

Both Raman spectroscopy and NIRS are molecular vibrational spectrum studying vibrational transitions in molecules [34,35]. However, the analytical theory involved in them differs. The former is a sort of scattering spectrum, while the latter is a kind of absorption spectra. Raman scattering (Fig. 2) can be obtained from the inelastic collision between the incident light photons from monochromatic light and molecular when the sample is exposed to light. Each substance has its own Raman spectra in feature. And it can be used to study the components and properties of the measured samples based on the unique frequency, intensity and polarization degree of spectrum. Also it is a complementary analytical tool to NIRS [17,36], as some chemical bonds with symmetrical charge distribution, such as C = C, S = S, whose infrared absorption is weak, can't be measured by infrared spectrometer, while the Raman spectrometer can well display the related information. Besides, it is suitable for the analysis of aqueous sample due to the weak absorption of water in Raman scattering.

As a novel analytical tool used for process monitoring, Raman spectroscopy has caused wide public concern over the global pharmaceutical industry [11]. It is featured by sharp lines due to molecular vibrations, which makes it available for quantitative analysis of the coating process [9]. The implementation of Raman spectroscopy in coating process is mainly used to determine drug contents and coating thickness, monitor drug polymorphic transformation and analyze coating uniformity, etc. Some statistical methods are commonly adopted to analyze the results obtained from the Raman spectra. Romero-Torres and coworkers measured the coating thickness of colored tablet by means of Raman spectroscopy combined with univariate and multivariate data analysis [11]. Besides, they employed partial least squares calibration model to quantify the variations within the tablets [24]. El Hagrasy and coworkers developed a quantitative model to predict the amount of tablet coating through the establishment of the correlation between Raman spectrum and average coating weight gain [37]. In addition, they also used Raman spectroscopy combined with multivariate calibration model to determine coating uniformity, and the calibration model is verified by tracking the coating progress of individual batches [9]. The Raman spectrum used for real-time monitoring of the coating process possesses the following advantages [11]: (1) it is easy to document vibration spectrum, which provides significant information on a complex mixture of components; (2) the integrity of measured samples could be maintained; (3) samples are allowed for no pretreatment; (4) remote analysis can be realized by collecting spectrum through optical fiber; (5) spectroscopy analysis can be performed via complex pattern recognition technology.

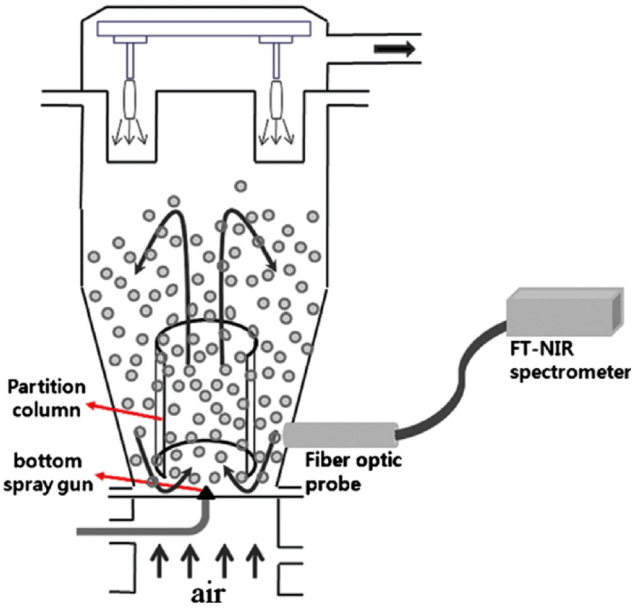

Fig. 3 – Schematic diagram of the fluid-bed coating process with NIR spectrometer (reproduced from Lee MJ et al. [32]).

Although the Raman spectroscopy technology used in the monitoring of coating process offers advantages, it has found limited use in practice for these and other applications due to the interfering fluorescence (Fig. 2), which is produced in many systems by the spontaneous emission of photos from low-lying excited electronic states [11]. As the fluorescence intensity is stronger than the Raman scattering intensity, the interfering fluorescence can mask Raman spectrum of vibrational shifts, thus affecting accuracy of the results, especially encountered for colored samples under visible excitation. To overcome this limitation, spectroscopists commonly employ excitation resources in the near infrared region (NIR) where the illuminating source has insufficient energy to reach most fluorescence-producing excited electronic state [11]. Additionally, when using Raman spectroscopy as an analytical tool to monitor the coating process, the analyst should be aware of these near infrared fluorescent substances, such as iron oxide, which is often incorporated in tablet core as a colorant.

3.3. *Laser-induced breakdown spectroscopy (LIBS)*

LIBS is a novel analytical tool, with high-energy pulse plasma emission spectrum produced by the interaction between laser and material elements analysis of new technology. Local high temperature in the measured samples (solid, liquid, gas) was generated due to the irradiation by high-power pulsed laser, leading to the formation of plasma plumage after excitation or ionization of atoms and molecules in the samples. Part of the energy can be emitted in the form of light during the process of relaxation of the excited atoms and ions in plasma. The radiation can keenly reflect the characteristics of elements, therefore, qualitative and quantitative analysis of the chemical elements in the samples can be performed according to the recorded spectrum which contains the specific radiation signal [38].

The LIBS technology has become mature after developments of several decades, and related researches on it have infiltrated into more and more fields, such as soil composition, mineral, metal compounds, polymers, cosmetics, etc [13]. However, there have been no reports in detail on the specific application of it in pharmaceutical industry. The currently reported applications of LIBS in the pharmaceutical industry include determination of excipients in the formulations [39,40], quantitative analysis of the API in solid dosage forms [41], evaluation of the distribution of magnesium stearate in the powder mixtures [42,43], investigation of the effect of physical properties of the samples on LIBS measurement [44], etc.

LIBS technology is featured by speed, which can allow it for online monitoring. Fig. 4 shows the schematic representation of LIBS instrument [14]. In the art of pharmaceutical coating, it can be used for on-line analysis of tablet coating thickness and coating uniformity. Mowery and coworkers have demonstrated the potential of LIBS technology in rapid characterization of film coating process [45]. In addition, Madamba and coworkers developed a LIBS method to rapidly analyze the coating thickness and uniformity in tablet coating used for photoprotection, explored the photoprotection mechanism in the coated formulation by means of a novel approach for the quantitative determination of the coating depth profile, and evaluated the feasibility of using this tool as a method to determine photostability of the drug substance through comparison with the results obtained from high performance liquid chromatography (HPLC) method [14]. Since the irradiation source used in LIBS is high-power pulsed laser, which generates a high local temperature in the measured samples, LIBS is a destructive analytical technology and not suitable in situations where samples needed to be reused [11,13].

4. Imaging techniques

The application of imaging techniques in the monitoring of coating process holds numerous superiorities: (1) data information can be obtained from multiple points of each sample, thus providing average information for the individual sample and reducing experimental error; (2) unlike the spectroscopy techniques, such as NIRS and Raman spectroscopy, it can realize depth detection of the samples; (3) compared with the results obtained from optical microscope, the analysis of coating uniformity is not only confined to a few points, but extended to the whole tablet surface; (4) compared with the traditional monitoring methods, it can allow for rapid analysis without destruction to the measured samples, and is time-/labor-saving. The currently reported imaging techniques for the monitoring of the coating process are displayed as following.

4.1. *Terahertz pulsed imaging (TPI)*

Terahertz is also referred to as far infrared, which spans from infrared to microwave in the electromagnetic spectrum, with the wavelength ranging from 30 μm to 3000 μm or from 100 GHz to 10 THz [1]. Compared with other imaging techniques, TPI technology is remarkably advantageous in

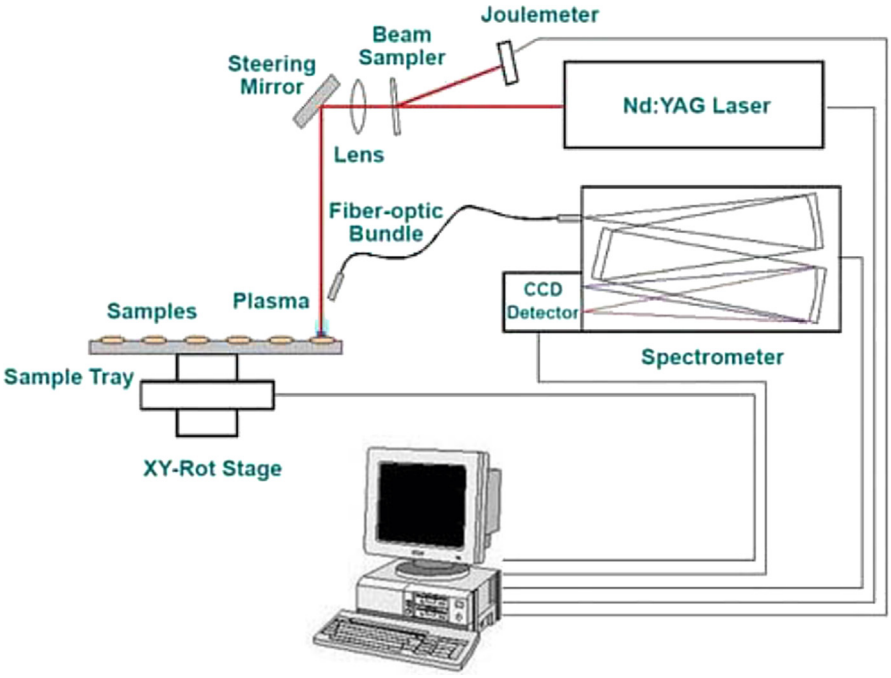

Fig. 4 – Schematic representation of LIBS instrument. LIBS indicates laser-induced breakdown spectroscopy; CCD, charged coupled device (reproduced from Madamba MC et al. [15]).

acquiring the amount of information. The acquired data set is actually three dimensional space-time data (three dimensional space axial (x, y) and one dimensional timeline). Terahertz images from a series of samples are available via these three dimensional data set [46]. TPI is a non-destructive measurement technique, and can be used to measure coating thickness on tablets. To measure the coating thickness, TPI works in this way [15], as shown in Fig. 5: since the coating layer is translucent to terahertz radiation, when the short pulses of terahertz radiation (half maximum full width (FWHM) < 1 ps) are focused on the coating tablet surface, part of the pulse can penetrate into the coating layer, and the other part of the pulse is reflected back to the detector. Furthermore, part of the pulses is reflected back where the refractive index

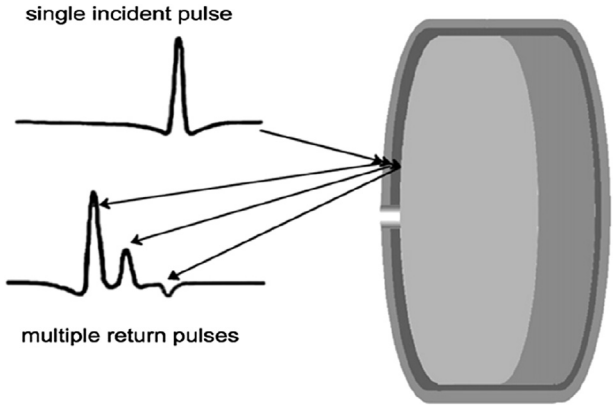

Fig. 5 – Schematic illustration of a single point TPI measurement (reproduced from Brock D et al. [14]).

of each interface changes, and can be detected as an additional reflected pulse. The coated thickness can be calculated according to the equation 2 dcoat = Δt c/n, wherein t is the delay time between the two reflected pulse, c is the speed of light, n is the refractive index of coating materials. The detailed information about the TPI measurement technology is provided by Zeitler and coworkers [47].

TPI technology offers major advantages over other analytical techniques used to study film coating, including: (1) compared with the LIBS technology, this technology is a completely non-invasive analytical tool, but possesses a similar depth resolution and a higher axial resolution [6]; (2) the average energy generated by this technology during analysis is low, thus causing no thermal damage to the samples [16], and enabling samples to be reused for some functional researches [6]; (3) any number of locations in the tablet can be probed by TPI, and the measurement can be extended to produce a three-dimensional map of the tablet. Meanwhile, the tablet uniformity can also be shown as a function of depth below the surface [6]; (4) it can not only provide similar information to that of NIRS and Raman spectra, but also extract detailed information on coating thickness due to the mapping established in the whole tablet surface [16]; (5) it is suitable for the analysis of single layer or multilayer complex coating due to the strong penetration capability of terahertz radiation, under the conditions where the coating thickness was more than 30 μm, which is associated with the measurement precision of this technology.

Since TPI is advantageous in many aspects, there is an increasing trend towards the developments of TPI as an advanced characterization tool for film coatings in the last decades. Ho and coworkers have demonstrated its capabilities

to construct 2D maps and 3D models of film coating defects and to determine coating uniformity [12]. In this study, TPI was validated by microscopic imaging with respect to the accuracy of measuring coating layer thickness. A new terahertz parameter (terahertz electric field peak strength/TEFPS) was also introduced by them to determine density of the tablet film coating [6]. Correlation of tablet coating thickness as measured by TPI with dissolution behavior was first reported by Spencer and coworkers [16].

Given the increasing amount of studies and use of the technique in industry, it is important to highlight some of the key measurement and signal processing considerations in more detail to avoid artifacts and thus ensure fully quantitative and robust TPI measurements. Brock and coworkers [48] has provided an insight into some critical factors when working with TPI (Table 2).

4.2. *Near infrared imaging*

Near infrared imaging technology is different from other spectral technology, as it can provide thousands of spectra but not just a single spectrum [1]. According to the literatures, the application of this technology in pharmaceutics includes determination of mixing homogeneity of the powder [49] and mixing uniformity of the end products [50], identification of tablet blister packaging [51], extraction information on the mixture of tablets and preliminary tablets [52]. Recently, it is also used to determine tablet content uniformity [53] and examine internal structure of the time-released granules [54]. However, there has been a few reports about its application on film coating [1]. Lene Maurer and coworkers employed the near infrared imaging and TPI technology to analyze the film coating process, and compared these two methods, concluding that they could provide similar information on the distribution of coating thickness, while TPI is more suitable for analysis of thick coating layer, and near infrared imaging has higher spatial resolution, thus enabling analysis of coating thickness under the TPI detection limit.

4.3. *Magnetic resonance imaging (MRI)*

The initial analysis of the performance of film coating is usually based on evaluation of casting film, such as elastic strength, wettability and dissolution behavior of the film in the standard release medium [55], etc. Up till now, there have been plenty of novel imaging techniques used for the evaluation of enteric coating system, such as acoustic microscopy, diffusive infrared microscopy, optical coherence tomography [56], etc. The application of these techniques is mainly focused on the analysis of thickness and continuity of the enteric coating [17], the disadvantage of which is that the comprehensive understanding of the coating process shall be carried out on a large amount of samples even at the beginning of the coating progress, and also is time and material consuming. Dorozynski P and coworkers [17] has adopted MRI technology as a novel method for rapid screening of the properties of these enteric coating compositions. Preparation of coated tablets in a fluidized bed is not essential by this method. The enteric coating model tablets were put in a specifically designed testing pool for component analysis. And the

Table 2 – Critical factors, causes, effects, and solutions in the measurement of tablet film coatings using terahertz pulsed imaging.

Critical factors	Causes	Effects	Solutions
Signal processing	Deconvolution settings	Distortions in the TPI signals	Correctly adjusting the pulse width (PW) and cut off frequency (CF).
Sample matrix	Crystallinity and particle size	Crystallinity: Oscillation in the time-domain waveforms acquired by TPI due to a change in n_{coat} Size: Scattering effects (At THz frequencies, Mie scattering can occur for particles or pore sizes >100 μm where the THz pulse undergoes a significant change in n_{coat} at the grain boundaries	Differentiation between oscillation artifacts from the deconvolution step and the genuine features of the sample matrix.
Signal distortions	Defects (a laser-drilled hole) and tablet edges	Defects: 1.Significant lose of scattering due to the strong local curvature of the tablet surface. 2. Low terahertz electric field peak strength (TEFPS) which describes the amplitude of the surface reflection relative to the ideal reflection measured using a mirror Tablet edges: 1. Lose of strong scattering 2. Reduced overall signal amplitude 3. Broaden peak features	Elimination of the drilling region and tablet edges to reduce the major effect on the standard deviation of layer thickness but only slightly influence the mean layer thickness values for the individual tablets.
Refractive index (n_{coat})	Changes in n_{coat} of different tablet density, batches, coating processes and process conditions	Contrasting peak directions	Using X-ray microtomograph ($X_{\mu}CT$) to accurately assess n_{coat} nondestructively directly on the investigated sample system.

feasibility of this method was confirmed in comparison with mini tablet dissolution results, thereby MRI technology can be used for the early screening of film coating formulations. The operations regarding this technology are simple, thus reducing the time required to screen coating formulations.

5. Microscopic techniques

Since the sensor sensitivity of PAT may be compromised or blurred with some "dirty" environment, they are not adaptable to all coating processes [5]. Some microscopic techniques, including confocal laser scanning microscope (CLSM), atomic force microscope (AFM), scanning electron microscope (SEM), etc. can be implemented off-line to extract useful information on coating process. Due to the destructive nature of these microscopic techniques except CLSM, they are not suitable for in-line monitoring of the coating process. However, SEM can be used as a validated method for TPI to determine coating thickness and coating surface, thus providing information on coating variability [11]. CLSM was determined to be a fast and effective analysis tool to quantify the coating thickness and distribution, and predict the coating functionality [32]. Besides, the CLSM data can be used to characterize the coating quality and the coating thickness to 1–1.5 μm [57]. Moreover, it can be used in a particular case where an autofluorescent agent is incorporated in the coating layer [4].

6. Film coating analysis

There have been various analytical tools to be implemented for the in-process monitoring of coating in the last decade. And their applications are generally aimed at: (1) measuring coating thickness and coating density, (2) determining process end point, (3) analyzing coating variability/uniformity, (4) plotting coating structure/morphology.

In measuring coating thickness, NIR and Raman spectroscopy are indirect measurement tools and likely to be more effective techniques to be employed in the case of immediate release coatings, where the coating film is thin, while they are sometimes restricted by their need for chemometric models and biased detection for the surface of the coating [50]. However, TPI, as a direct measurement tool, is only suitable for the analysis of tablet coating with a minimal coating thickness of 30–40 μm [58] due to low lateral resolution limit of 150–200 μm which makes small samples with a high curvature more challenging because of diffuse scattering effects [59]. Therefore technological advances for automated analysis of e.g. standard size pellets are desirable, but coating thickness of a single pellet is not of such importance when pellets are compressed into tablets or filled in capsules to produce multi-unit dosages forms. Unlike the spectroscopic techniques, TPI has the capability to resolve multiple coating layers with a single-point measurement and may not require the set-up and maintenance of robust multivariate analysis models for data interpretation [19,60]. Besides, TPI can be used to directly measure coating density based on the density differences between the two tablets surfaces and the centre band due to distinct differences of the peak orientation in the terahertz waveform [61]. Generally, a coating/core minimum indicates a higher n (refractive index) of the coating material than of the core and conversely, a maximum indicates a lower n of the coating material compared to the core [59]. Some destructive techniques, such as LIBS and SEM, can be introduced as reference or validation methods for the estimation of coating thickness. While in MRI the signals are only acquired during dissolution and thus information on the coating quality can only be obtained indirectly [62].

The determination of coating end point of solid dosage forms in an industrial process should be possible with these spectroscopic methods, especially NIR and Raman spectroscopy, which will be implemented in greater extent [19]. It can be performed as a result of predicting coating thickness.

For the determination of coating variability/uniformity, both NIR and Raman spectroscopy are ideal tools due to high-speed analysis and chemical selectivity [3]. LIBS is also introduced to rapidly and inexpensively investigate inter/intra-tablet coating variability by assigning an average coating score based on the obtained data despite its destruction to the measured samples [13]. Since the terahertz maps acquired by TPI consist of over one thousand pixels providing detailed information on the coating thickness distribution, coating uniformity is concomitantly determined [12]. SEM also provides the possibility to detect intra-tablet or intra-pellet variation in coating thickness after measured samples cutting into halves [19].

In mapping of coated products, TPI holds superiorities over those spectroscopic techniques, as any number of locations in the tablet can be probed [6], and even interfaces located up to 2 mm below the tablet surface of coated tablets can be detected due to deep penetration [58]. Besides, a three-dimensional map of the coated tablet is achievable as a function of the obtained three dimensional data set, and thus coating defects like craters, scratches, surface roughness and drilled holes (in the case of a push–pull osmotic system) could be detected [19].

7. Conclusions

Film coating which has emerged as early as 1950s, represents an important unit operation for producing solid dosage dorms, while the implementation of "PAT" for monitoring of this pharmaceutical coating process is still in the experimental stage. The "PAT" guidance was first put forward by the FDA, with the ultimate goal to efficiently produce products of high quality. The quality of the final products can be affected by a myriad of processing parameters in the coating process, such as temperature of the inlet and outlet air, pressure of the inlet and outlet air, flow rate, spraying rate, etc. These parameters are difficult to maintain at a particular level in the actual operation process, which is likely to inflict coating variability between inter-/intra-tablets. While the traditional method used to monitor the coating process has many shortcomings, so it is necessary to develop some novel technology for rapid monitoring of the coating process and improvement in the production efficiency, thus creating better economic benefits.

The application of PAT on film coating was mainly focused on measurement of the amount of coating and coating

thickness, determination of the coating endpoint and coating uniformity, mapping of the coated products, etc. Whereas, these techniques are not suitable for all the coating processes, as the sensitivity of the sensor may be blurred with dirty coating environment and product attributes, resulting in failure to obtain valuable data information. Although it is believed that the implementation of PAT is a promising approach to in-process monitor film coating, more in-depth researches are required for the transition of these technologies from laboratory scale to industrial scale.

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