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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