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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

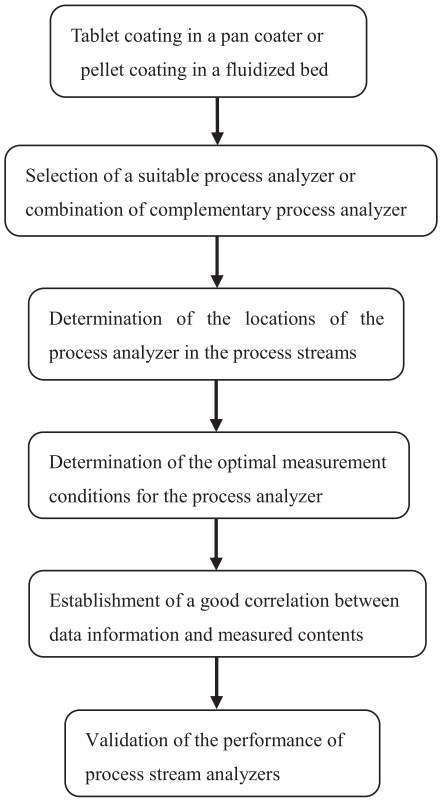

Fig. 1 – Major steps to establish process analytical technologies.