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A study on the applicability of in-line measurements in the monitoring of the pellet coating process

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ABSTRACT

Special populations including paediatric and elderly patients often need advanced approaches in treatment, such as one-a-day dosing, which is achieved with modified release formulations or alternative routes of applications such as nasogastric route. Pellets are a dosage form that is frequently used in such formulations.

The aim of the present work was to study the applicability of two in-line techniques, namely, Near Infrared Spectroscopy (NIR) and Spatial Filtering Technique (SFT) in the pellet coating process. The first objective of our work was to develop a prediction model for moisture content determination with the in-line NIR and to test its robustness in terms of sensitivity to changes in composition of the pellets and performance in wide range of moisture content. Secondly, the in-line SFT measurement was correlated with different off-line particle size methods. The third objective was to evaluate the ability of both in-line techniques for the detection of undesired deviations during the process, such as pellet attrition and agglomeration. Finally, the ability to predict coating thickness with the in-line NIR probe was evaluated.

Results suggested that NIR prediction model for moisture content was less robust outside the calibration range and was also sensitive to changes in composition of the film coating. Nevertheless, satisfactory prediction was achieved in the case when coating composition was partially altered and adequate calibration range was used. The SFT probe results were in good correlation with off-line particle size measurement methods and proved to be an effective tool for coating thickness determination during the coating, however, the probe failed to accurately show the actual amount of the agglomerates formed during the process. In experiment when pellet attrition was initiated, both probes successfully detected abrasion of the pellet surface in real time. Furthermore, a predictive NIR model for coating thickness was made and showed a good potential to measure coating thickness in-line, suggesting that the NIR probe can be used as a single tool to monitor water content, coating thickness, and deviations in the coating process.

1. Introduction

Multi particulate systems offer many advantages over single unit matrix systems or coated tablets in terms of safety and efficacy, such as lower occurrence of dose dumping and lower inter-subject variability when modified drug release is needed (Bechgaard and Nielsen, 1978). Furthermore, alternative routes of administration such as nasogastric tubes can be used with such formulations (Toedter Williams, 2008). This is especially important in case of special populations such as elderly or paediatric patients.

Coated pellets are the most common type of multi particulate systems used in modified release formulations. The essential step of pellet production is coating of pellets with functional coating. This is usually performed by bottom spray fluidized bed coating technology. Strict control of the coating process is required since the performance of modified release coating is directly correlated with in-vivo performance of the formulation.

In the recent years a number of new techniques enabling real-time monitoring of the process emerged as a consequence of new approach in development and production of pharmaceutical products called Quality by Design (QbD). QbD is described in Quality guidelines (Q8, Q9, and Q10) of The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH, 2009, 2005, 2008).

Near Infrared Spectroscopy (NIR) is one of techniques that is most commonly researched in the field of Process Analytical Technology (PAT) (FDA, 2004), which is an essential part of QbD. Numerous publications are published covering the use of in-line

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NIR in almost all production steps of solid dosage forms these being from blending process (Berntsson et al., 2002), granulation process (Rantanen et al., 2000), tableting process (Karande et al., 2010), and tablet coating process (Perez-Ramos et al., 2005). Several publications also investigate important pellet characteristics in the pellet coating process, such as moisture content (Mantanus et al., 2009), coating thickness (Lee et al., 2011; Avalle et al., 2014), and drug release profile (Pomerantsev et al., 2011). However, there still remains a need to further investigate the ability of in-line NIR to predict multiple pellet characteristics and to evaluate the robustness of NIR models.

The other frequently studied area of PAT are in-line particle size measurement techniques. These include optical techniques which measure chord length of particles, such as Focused Beam Reflectance Measurement (FBRM) and Spatial Filtering Technique (SFT), and different image analysis approaches (Silva et al., 2013; Kadunc et al., 2014). Use of passive acoustic emission technique to measure particle size is also described in the literature (Poutiainen et al., 2012). In contrast to the above mentioned techniques which measure particle size, Terahertz Pulsed Imaging (TPI) can be used to directly determine coating thickness as well as coating surface roughness. Most publications describe off-line use of TPI to determine coating thickness on pellets (Haaser et al., 2012) or tablets (Ho et al., 2009, 2008, 2007), although one publication also describes an in-line use of TPI to measure coating thickness during tablet film coating process (May et al., 2011).

Most publications evaluate the use of FBRM and SFT in fluid bed granulation process in comparison to traditional off-line techniques. Good correlation can be obtained although absolute values of particle size differ due to different measuring principles (Närvänen et al., 2009; Hu et al., 2008). Recently an article comparing FBRM and SFT performance has been published. Authors concluded that both techniques show similar trends in particle size growth (Kukec et al., 2012). In another recent publication authors study the use of SFT in pellet coating. A correlation with Dynamic image analysis is made showing good correlation between techniques. The influence of process parameters and key SFT measurement setting (Particle buffer) on measurement results is discussed. Authors concluded that Particle buffer setting has an important impact on measured particle size values (Folttmann et al., 2014).

Although in-line particle size measurements could be very useful in pellet coating process for evaluating coating thickness and also undesirable processes, such as agglomeration and pellet attrition, there is still very little research in this area.

The objective of the present work was to study the applicability of in-line measurements in the process of pellet film coating. In-line NIR data were correlated with different off-line methods for moisture content determination, models for moisture content prediction were set, and later moisture content in pellets with different film coating compositions was predicted. Furthermore, NIR data were correlated with in-line particle size measurements in order to predict coating thickness using a PLS model. Robustness of NIR models was investigated by changing the composition of the film coating and by simulating process deviations that could occur in the production environment. The second objective of the present work was to correlate SFT in-line particle size measurements with different off-line particle size determination methods and to use in-line results for evaluation of coating thickness, pellet agglomeration, and pellet attrition.

The study of SFT and NIR in-line tools should contribute to a better understanding of the PAT applicability in the monitoring, controlling, and designing of modified release pellet coating processes. Firstly, such tools enable efficient coating thickness control and hence better active ingredient dissolution repeatability. In addition, better stability and consistent final product quality is achieved through real time moisture content management. Paediatric and geriatric patients are especially vulnerable to different health issues, thus, manufacturing of medicine at the highest quality level, with the help of PAT tools, can improve the quality of their lives.

2. Materials and methods

2.1. Manufacturing of the film coated pellets

In our study six pilot scale batches of film coated pellets were produced and phase of controlled release film coating application onto the drug layer pellets was precisely examined. Drug layered pellets comprised hydroxypropyl cellulose (Klucel™ EF, Ashland Inc., USA), diclofenac sodium (Krka, d.d., Slovenia), and talc (Imerys Talc, Italy) applied on the neutral sugar pellets (Hanns G. Werner, GmbH + Co., Germany). Drug layered pellets were further film coated. Controlled release coating compositions of batches No. 1, 2, 5, and 6 were identical, while compositions of the third and fourth batch were modified in comparison to the other batches. Quantitative composition of the film coating dispersion was changed in the third batch and polymer type was altered in the fourth batch, i.e. qualitative variation. Compositions of different experiments are shown in Table 1. All of the coating dispersions comprised polymethacrylic coating polymer (Eudragit® RL, RS or L 30D, Evonik Industries, Germany), triethyl citrate (Vertellus Performance Materials, USA), and talc (Imerys Talc, Italy). Purified water was used as a dispersing medium. Pellets were coated in the Aeromatic-Fielder™ MP 3/2/4 fluid bed processor (GEA Pharma Systems, Switzerland), on which the bottom spray

Table 1
Compositions of the individual batches.

Component	Function	Batches No. 1, 2, 5, 6	Batch No. 3	Batch No. 4
Eudragit RS 30 D	Controlled release polymer	1.0 kg (4.8%)	2.37 kg (16.3%)	–
Eudragit RL 30 D	Controlled release polymer	1.0 kg (4.8%)	0.59 kg (4.1%)	–
Eudragit L 30 D	Delayed release polymer	–	–	2.0 kg (9.6%)
Talc	Anti-tacking agent	0.30 kg (1.4%)	1.15 kg (7.9%)	0.30 kg (1.4%)
Triethyl citrate	Plasticizer	0.078 kg (0.38%)	0.17 kg (1.2%)	0.078 kg (0.38%)
API layered pellets	Active ingredient carrier	5.0 kg (24.1%)	4.0 kg (27.5%)	5.0 kg (24.1%)
Purified water	Dispersing medium	13.39 kg (64.5%)	6.26 kg (43.1%)	13.39 kg (64.5%)