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Applicability of near-infrared spectroscopy in the monitoring of film coating and curing process of the prolonged release coated pellets

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ABSTRACT

Although process analytical technology (PAT) guidance has been introduced to the pharmaceutical industry just a decade ago, this innovative approach has already become an important part of efficient pharmaceutical development, manufacturing, and quality assurance. PAT tools are especially important in technologically complex operations which require strict control of critical process parameters and have significant effect on final product quality. Manufacturing of prolonged release film coated pellets is definitely one of such processes. The aim of the present work was to study the applicability of the at-line near-infrared spectroscopy (NIR) approach in the monitoring of pellet film coating and curing steps. Film coated pellets were manufactured by coating the active ingredient containing pellets with film coating based on polymethacrylate polymers (Eudragit® RS/RL). The NIR proved as a useful tool for the monitoring of the curing process since it was able to determine the extent of the curing and hence predict drug release rate by using partial least square (PLS) model. However, such approach also showed a number of limitations, such as low reliability and high susceptibility to pellet moisture content, and was thus not able to predict drug release from pellets with high moisture content. On the other hand, the at-line NIR was capable to predict the thickness of Eudragit® RS/RL film coating in a wide range (up to 40 μm) with good accuracy even in the pellets with high moisture content. To sum up, high applicability of the at-line NIR in the monitoring of the prolonged release pellets production was demonstrated in the present study. The present findings may contribute to more efficient and reliable PAT solutions in the manufacturing of prolonged release dosage forms.

1. Introduction

In the beginning of the century the Food and Drug Administration announced a new initiative, Pharmaceutical Current Good Manufacturing Practices (CGMPs) for the 21st Century, to enhance and modernize the pharmaceutical manufacturing and product quality (FDA, 2004a). One of the key objectives of the initiative is to encourage pharmaceutical industry to implement new technologies, such as process analytical technology (PAT) in the development and manufacturing of pharmaceuticals. PAT 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). Process analysers for in-process generation of large amount of (multivariate) data are considered as one of the essential PAT tools. In the recent years, Near-infrared (NIR) spectroscopy has been the most frequently used process analysing technique in the field of pharmaceutical technology since it can be used in a variety of solid dosage forms manufacturing stages, e.g. granulation (Chablani et al., 2011), blending (Momose et al., 2011), tabletting (Karande et al., 2010), and film coating (Gendre et al., 2011; Lee et al., 2011). In the present study, the NIR was used to evaluate its applicability for monitoring and analysing film coating and curing process with the polymethacrylate polymer.

Solid pharmaceutical dosage forms are coated for decorative, protective, and functional purposes. One of the most common reasons for the application of polymeric coating is to alter the release characteristics of drugs (Felton, 2007). Coating thickness and curing step conditions play crucial roles in controlling drug release from sustained-release dosage forms (Shao et al., 2002). Coating thickness effect on drug release rate can be rather straightforward, but the impact of curing step conditions can be much more complex and difficult to understand. Curing step is considered as the post-coating treatment of polymer film that facilitates formation of a continuous coating. Continuous film is achieved through the following three phases: evaporation and particle ordering, particle deformation, and interdiffusion across polymer/polymer boundaries (Keddie, 1997; Steward et al., 2000; Felton, 2013). Many factors, such as curing time, temperature, relative humidity, amount and type of plasticizer, and coating level, affect the polymer film formation and consequently drug release rate. Increased harshness of the curing conditions

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(time, temperature, and relative humidity) usually increases curing effect and indirectly reduces drug release rate. In addition, the effect of curing conditions depends strongly on plasticizer used and on coating level (Yang et al., 2010). Plasticizer effect on curing phenomenon was also shown by Hamed and Sakr (2003) who also suggested that prolonged curing can lead to faster release profiles due to active ingredient migration into the film coating. Williams and Liu (2000) showed than not only curing time, temperature and relative humidity but also coating conditions impact the extent of final coalescence. Since dissolution is only an indirect measure of the curing level, determination of direct curing effect on physical-mechanical properties of the film (e.g., glass transition temperature, force of adhesion, strength and elasticity of the film) is also of great importance (Felton and Baca, 2001; Parikh et al., 1993).

The NIR is multivariate and non-destructive measuring principle allowing the acquisition of large data quantity in very short time intervals. Since NIR spectra contain extensive amount of physical and chemical information, the NIR can be useful tool to directly measure the extent of continuous polymer film formation (Gendre et al., 2012; Gendre et al., 2013). With the application of multivariate data analysis (MVA) tools measured spectral information can be used not only for the evaluation of the curing level but also for real-time prediction of curing related properties, i.e. physical-mechanical film properties and drug release rate. Nevertheless, the number of studies in this field is rather limited (Howland and Hoag, 2013; Howland et al., 2015; Tabasi et al., 2008). Tabasi et al. (2008) compared the NIR results to more conventional methods of dynamic scanning calorimetry (DSC) and hot stage microscopy (HSOM) and they showed that the extent of curing correlated with the convergence of the 1908 nm peak. Furthermore, the authors developed and validated the 7-factor PLS (partial least squares) model for the prediction of the amount of theophylline release at 250 min from Eudragit® RL:RS (1:4 ratio) coated tablets cured at different time periods at 40 °C. However, the authors stated they had difficulties to predict theophylline release from tablets cured at 50 °C. Howland and Hoag (2013), as well as Tabasi, detected a reduction of the 1908 nm peak as curing of the Eudragit® cast films progressed. Moreover, the authors developed a PLS models that related NIR spectra to the variation of physical-mechanical film properties and were able to predict Young's Modulus, which indicated the extent of curing. In another study, Howland et al. (2015) found that spectral changes were related to changes associated with glyceryl monostearate during curing and they developed a PLS model for the prediction of the extent of curing and the final state of glyceryl monostearate post curing. Gendre et al. (2012, 2013) showed that two characteristic water bands, i.e. 5060–5380 cm^{-1} and 6970–7190 cm^{-1}, varied during both static and dynamic curing process of ethyl cellulose coated tablets and suggested that spectral variation correlated with the removal of water trapped within the coating layer. However, the authors detected no other spectral variations that could be linked directly to curing. Latter research suggests that also 1908 nm (5241 cm^{-1}) peak variation that was linked to curing phenomenon of Eudragit® RL:RS film coating (Howland and Hoag, 2013; Tabasi et al., 2008) could be actually a consequence of the removal of water from the film coating.

In the present study, the applicability of the NIR for the determination of active ingredient release rate as a function of the curing extent was evaluated. Active ingredient containing pellets film coated with the Eudragit® RS/RL prolonged release coating were used as a model dosage form. The PLS model for the release profiles prediction of pellets cured in a wide range of curing conditions was calibrated, which enabled adequate release profiles prediction of the independent data set. Relationship between spectral data and drug release profiles was discussed. To the best of the authors' knowledge, there have been no published studies investigating the usability of the NIR for the prediction of an active ingredient release profiles due to the curing effect yet. In addition, correlation of the spectral data with the pellet moisture content was determined in order to clarify what is the suitability of the 1908 nm peak for drug release modelling and what is the effect of high moisture content on the predictive power of the PLS model.

Moreover, Eudragit RS/RL pellet coating thickness with the at-line NIR was determined in the present study. Pellet coating thickness and thickness related pellet characteristics have already been investigated in the published literature. Andersson et al. (2000) successfully predicted ethyl cellulose (EC) coating thickness with the in-line NIR diffuse reflectance fiber probe. Similarly, a decade later the applicability of the in-line NIR probe for hydroxypropyl methylcellulose coating thickness was presented (Lee et al., 2011). Coating thickness of controlled release polymer affects drug release profiles and NIR can be therefore also used for in-line drug release profiles prediction (Pomerantsev et al., 2011). In the recent studies, Marković et al. (2014) showed that in-line probe can be used for monitoring of multiple characteristics of the enteric coated pellets, including coating thickness, and Hudovornik et al. (2015) demonstrated the possibility for in-line prediction of Eudragit® RS/RL coating thickness. The significance of at-line NIR measurement for pellet coating process evaluation was demonstrated by Avalle et al. (2014) who showed high applicability for monitoring of the active ingredient coating (coating thickness, assay) and controlled release coating (coating thickness, dissolution performance). Despite the fact that pellet coating thickness has already been measured with at-line and in-line NIR before, our study demonstrated that both film coating and curing can be monitored in at-line NIR environment suggesting that this measuring principle can form an important part of the complete PAT solution for the production of prolonged release coated pellets.

2. Materials and methods

2.1. Preparation of the film coated pellets

Drug layered pellets comprising hydroxypropyl cellulose (Klucel™ EF, Ashland Inc., USA), diclofenac sodium (supplied by Krka, d.d., Slovenia), and talc (Imerys Talc, Italy) applied on the neutral sugar pellets (Hanns G. Werner, GmbH + Co., Germany) were used as a carrier material for the film coating process. Drug layered pellets were film coated with the coating dispersion consisting of polymethacrylic coating polymer (Eudragit® RL 30D and RS 30D, Evonik Industries, Germany), triethyl citrate (Vertellus Performance Materials, USA), talc (Imerys Talc, Italy), and purified water as a dispersing medium. Compositions of film coatings (weight/weight % of dry material) used in the study are presented in Table 1.

Film coated pellets for the purpose of curing phenomenon evaluation were prepared in Glatt GPCG-3 fluid bed coater using a bottom spray coating insert. Coating conditions during the process were: inlet air temperature 45–55 °C, product temperature 29–30 °C, fluidization airflow 80–100 m^3/h, spray rate 25–45 g/min, and atomizing air pressure 2.0 bar. At the end of the spraying phase, pellets were dried at an inlet air temperature of 50 °C for 5 min. 10% of polymer coating by weight of the drug layered pellets was applied during the process. One batch of film coated pellets was produced for the purpose of curing process evaluation.

Film coated pellets for the purpose of coating thickness evaluation were film coated in the Aeromatic-Fielder™ MP 3/2/4 fluid bed processor (GEA Pharma Systems, Switzerland) with the bottom spray

Table 1
Compositions of film coating dispersions (% by weight of dry material) used for curing and film coating thickness experiments.

Component	Evaluation of curing	Evaluation of film coating thickness
Eudragit RS 30 D	55.40%	42.05%
Eudragit RL 30 D	13.85%	42.05%
Talc	26.84%	12.62%
Triethyl citrate	3.91%	3.28%