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In-line Raman spectroscopic monitoring and feedback control of a continuous twin-screw pharmaceutical powder blending and tableting process

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ABSTRACT

The integration of Process Analytical Technology (PAT) initiative into the continuous production of pharmaceuticals is indispensable for reliable production. The present paper reports the implementation of in-line Raman spectroscopy in a continuous blending and tableting process of a three-component model pharmaceutical system, containing caffeine as model active pharmaceutical ingredient (API), glucose as model excipient and magnesium stearate as lubricant. The real-time analysis of API content, blend homogeneity, and tablet content uniformity was performed using a Partial Least Squares (PLS) quantitative method. The in-line Raman spectroscopic monitoring showed that the continuous blender was capable of producing blends with high homogeneity, and technological malfunctions can be detected by the proposed PAT method. The Raman spectroscopy-based feedback control of the API feeder was also established, creating a 'Process Analytically Controlled Technology' (PACT), which guarantees the required API content in the produced blend. This is, to the best of the authors' knowledge, the first ever application of Raman-spectroscopy in continuous blending and the first Raman-based feedback control in the formulation technology of solid pharmaceuticals.

1. Introduction

Continuous pharmaceutical manufacturing, both at upstream (API production) and downstream (formulation technology) processing, is rapidly gaining interest as a promising way to improve efficiency, reduce operating costs and ensure easier scale-up and shorter time-to-market (Plumb, 2005). Nevertheless, conversion from batch to continuous manufacturing entails the necessity of continuous process monitoring and an integrated quality control strategy. Real-time quality assurance of continuously manufactured products must be developed in order to be able to implement continuous manufacturing processes, the future of pharmaceutical manufacturing (Rantanen and Khinast, 2015). Its implementation is supported by the Process Analytical Technology (PAT) (FDA, 2004) and Quality by Design (QbD) (ICH, 2009) guidelines, which encourage the application of in-line process analyzers, for instance vibrational spectroscopic probes to enable knowledge-based and efficient pharmaceutical manufacturing.

Raman spectroscopy has already been utilized several times as a process analyzer throughout the manufacturing processes of solid dosage formulations (Esmonde-White et al., 2017; Paudel et al., 2015), although the number of applications still considerably lags behind Near-Infrared (NIR) spectroscopy (De Beer et al., 2011). However, mainly batch processes were monitored, such as wet granulation (Wikstrom et al., 2005), fluid bed drying (Kogermann et al., 2008), freeze drying (De Beer et al., 2009), or end-point detection of tablet coating (Müller et al., 2010). A recent review (Fonteyne et al., 2015) showed that there are few PAT applications with continuous manufacturing, out of which the utilization of Raman spectroscopy is negligible. Raman and NIR spectroscopy have also proved their applicability to characterize tablet properties, such as tensile strength (Casian et al., 2017) or quantify crystalline (Vervaeck et al., 2015) and polymorph content (Nagy et al., 2016; Tian et al., 2007) of pharmaceuticals. These properties directly influence the drug release rate, therefore their effective in-

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line monitoring and control could eventually lead to real-time release testing.

Powder blending is one of the most fundamental unit operations in the production of multicomponent solid dosage forms, therefore its effective execution and control is crucial to ensure the quality of the end-product, *e.g.* content uniformity of tablets. Continuous blenders, such as ribbon blenders have been known in various fields of chemical engineering, and their properties have been extensively characterized both theoretically and experimentally (Osorio et al., 2015; Pernenkil and Cooney, 2006; Portillo, 2008; Teżyk et al., 2016). The feasibility of continuous mixing of pharmaceuticals has also been confirmed by taking into consideration pharmaceutical quality control and sensitivity issues (Berthiaux et al., 2008). Nevertheless, only a limited number of studies have been conducted about PAT in continuous blending. In a comprehensive study (Pernenkil, 2008), NIR and Light Induced Fluorescence (LIF) analysis were used with continuous ZigZag® and double helical ribbon blender experiments. Vanarase et al. developed NIR methods for in-line monitoring of acetaminophen concentration and homogeneity in a pharmaceutical blend (Vanarase et al., 2010; Vanarase and Muzzio, 2011). Furthermore, the analytical error of the in-line, multipoint NIR measurement and the real-time measured unit dose were determined (Vanarase et al., 2013a), and a quantitative method was applied for the analysis of the residence time distribution (RTD) (Vanarase et al., 2013b). Fonteyne et al. performed the continuous blending of theophylline and lactose on a twin-screw granulator and used a calibration free moving F-test method for the analysis of NIR spectra (Fonteyne et al., 2016). In contrast, thorough search of the relevant literature yielded no Raman spectroscopic studies in continuous powder blending, despite its several successful batch applications (Allan et al., 2013; De Beer et al., 2011, 2008; Hausman et al., 2005; Vergote et al., 2004).

Although the PAT initiative (FDA, 2004) encourages process control based on the real-time acquired data, a small part of PAT applications goes beyond monitoring the processes and follows the PACT ('Process Analytically Controlled Technology') approach. The vast majority of studies conducted for PAT is only used for the better understanding of the production and conclude that the proposed analytical method could be further utilized for control strategies. However, such work needs the close cooperation of experts in pharmaceutical technology, process control, analytics, chemometrics and informatics, which is still a rarely resolved issue. Moreover, such control principles could also conflict with the traditional, rigid quality assurance procedures of pharmaceutical companies, which further hinder their actual utilization.

Regarding Raman spectroscopy-based control, a feedback control has been utilized for an oximation reaction (Csontos et al., 2015), as well as for the crystallization of carvedilol polymorphs (Pataki et al., 2013). In the field of bioprocesses, lactose concentration during lactose hydrolysis (Hirsch et al., 2016) and concentration of lactate in mammalian cell culture (Matthews et al., 2016) were controlled by Raman spectroscopy. Nevertheless, to the best of the authors' knowledge, Raman spectroscopy has not yet been utilized for the control of solid pharmaceutical formulation processes.

In the present study, a two-step continuous manufacturing line, *i.e.* a powder blending followed by direct tableting, is introduced. A three-component model pharmaceutical formulation including caffeine, glucose and magnesium stearate was analyzed in real-time by Raman spectroscopy and a quantitative method has been developed for the determination of caffeine content in the powder blend and tablets. This method allows a real-time content uniformity test to be performed and derive the composition of the powder from the Raman spectroscopic measurements in a closed-loop control of the powder feeders. In addition, it was also studied whether the off-line developed quantitative method could be utilized for the evaluation of real-time acquired spectra. Then, the feasibility of Raman spectroscopy to detect deviations in the blending process (such as inadequate feeding or blending) and controlling the blend composition was assessed.

This is the first application of Raman spectroscopy for real-time study of a continuous pharmaceutical blending process and the first Raman-based feedback control in the formulation technology of pharmaceutical solid dosage forms. A conventional control strategy of feeding, for example gravimetric feeding with controlled material feed rates can greatly benefit from such analysis and, if necessary, control, as in this case malfunctioning of the gravimetric feeding or the following blending step, can also be handled. This provides additional quality assurance which is crucial, for instance, for achieving real-time release of the product.

2. Materials and methods

2.1. Materials

The continuous blending experiments were conducted using anhydrous caffeine as the model active pharmaceutical ingredient (API) and glucose monohydrate as the excipient. Before tableting, magnesium stearate was added directly to the punch tips and die walls for lubrication. Anhydrous caffeine was supplied from BASF (Ludwigshafen, Germany), glucose monohydrate was a kind gift of Hungrana Ltd. (Szabadegyháza, Hungary) and magnesium stearate was provided by Faci S.P.A (Carasco, Italy). The Raman spectra of the raw materials are depicted in Fig. 1.

2.2. Continuous manufacturing line set-up

The experimental set-up of the continuous blending and tableting process is illustrated in Fig. 2. A continuous twin-screw multipurpose equipment, TS16 QuickExtruder® (Quick 2000 Ltd, Hungary) was used, which is suitable for continuous homogenization, wet granulation and melt extrusion. A screw diameter of 16 mm (25 L/D ratio) was used at 70 rpm to mix caffeine (model API) and glucose (excipient). Caffeine and glucose were added via single-screw and twin-screw volumetric feeders (Quick 2000 Ltd, Hungary), respectively. The glucose feeding rate (*approx.* 400–800 g/h) was changed manually while the automatic control of caffeine feeding (*approx.* 0–100 g/h) was accomplished through the implementation of an in-house developed USB interface. This device creates a connection between the controlling computer and the feeder by converting a PID (proportional-integral-derivative) control signal to voltage ranging between 4 and 12 V, which changes the feeding rate.

The constituents were homogenized in the twin-screw blender. After the powder blend left the blender, a conveyor belt carried the

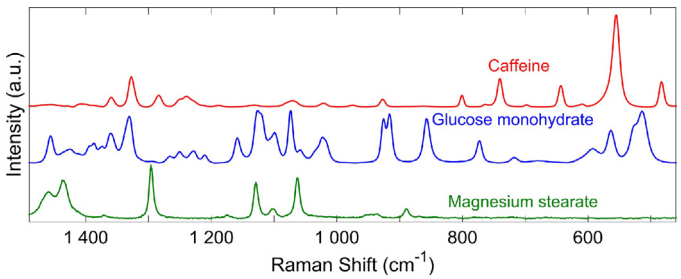

Fig 1. Reference Raman spectra of the raw materials. Intensity is in arbitrary unit, spectra are normalized and shifted to facilitate visual comparison of peak positions.