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Research paper

Analysis of the dehydration process of caffeine using backscattering and transmission Raman spectroscopy

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ABSTRACT

In the present study, the dehydration process of caffeine hydrate (CAH) was investigated by calibrating the moisture content in the caffeine tablet using backscattering Raman spectroscopy (BRS) and transmission Raman spectroscopy (TRS). The detectable depth of BRS is limited by its shallow laser penetration, while TRS is a powerful tool to determine the content of active pharmaceutical ingredients in a tablet. Our results suggest that the accuracy of a TRS-based calibration model falls beyond that of a BRS-based model. Based on the calibration used, the model was built by calculating the differences in the crystalline structures between hydrate and anhydrous caffeine. Moreover, it was demonstrated that the dehydration process occurred by switching water molecules between hydration sites of caffeine.

1. Introduction

Pseudo-polymorphism affects the dissolution characteristics and the bioavailability of substances in drug formulations (Debnath and Suryanarayanan, 2004; Shefter and Higuchi, 1963; Zografi, 1988). During the pharmaceutical manufacturing process, polymorphic changes can have a significant impact on dissolution properties (Haleblian and McCrone, 1969; Otsuka et al., 1997, 2013; Sakata et al., 2005). Most pharmaceutical manufacturing processes are carried out in batches due to strict regulations (Peeters et al., 2016; Fonteyne et al., 2013).

However, the Food and Drug Administration (FDA) has recently introduced the process analytical technology (PAT) initiative, which embodies the monitoring of the production process of the 21st century's pharmaceutical good manufacturing practice (GMP) (FDA, 2004). The initiative has attracted a lot of attention as a means of improving the quality of a pharmaceutical formulation, in order to guarantee the overall quality of the final product through system management, analysis, and introduction of new manufacturing technologies for achieving more efficient processes (Peeters et al., 2016; Fonteyne et al., 2013; Hinz, 2006; Eliasson et al., 2008).

The ultimate goal of the PAT initiative is to open the "*black box*" in the manufacturing process in order to enhance process understanding and to assist in identifying and controlling critical points in a process (Otsuka et al., 2014). For instance, significant variations in moisture contents take place during the kneading and drying process, resulting in a pseudo-polymorphic transition between the anhydrous and hydrate forms of bioactive compounds. The implementation of PAT systems is important to monitor and control these transitions and ensure product quality (Hédoux et al., 2015; Johansson et al., 2007; Matousek and Parker, 2006; Morris et al., 2001).

Caffeine hydrate (CAH) converts to anhydrous caffeine under low humidity environment (Otsuka et al., 2009; de Matas et al., 1998; Krzyzaniak et al., 2007; Hédoux et al., 2015). The crystalline structures have previously been determined using single crystal x-ray diffraction (Jørgensen et al., 2002; Krzyzaniak et al., 2007; Otsuka et al., 2009; Uchida and Otsuka, 2011). A number of reports have been published on pseudo-polymorphic transition using near-infrared (NIR) (Jørgensen et al., 2002; Krzyzaniak et al., 2007; Otsuka et al., 2014; Uchida and Otsuka, 2011), infrared (IR) (Bagheri et al., 2014), and Raman spectroscopy analyses (de Matas et al., 1998; Jørgensen et al., 2002), which all qualify as non-destructive and non-contact measurement methods, in line with the PAT scheme. Both the IR and NIR spectroscopy are sensitive to vibrational modes, including hydrogen bonds such as O—H and C—H. On the other hand, Raman spectroscopy is sensitive to vibrational modes associated with molecular frames such as C—C. Hence IR and NIR measurements are useful to monitor changes in water contents, while Raman spectroscopy is effective in detecting

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changes in crystalline structure during dehydration or hydration (Eliasson et al., 2008; Griffen et al., 2015, 2016). Additionally, Raman spectroscopy is commonly used to determine the quality of solid formulation components and identification of products (Hargreaves et al., 2011; Zhang and McGeorge, 2015).

In order to ensure that the incorporation of an active pharmaceutical ingredient (API) into a tablet is performed in a reproducible manner, transmission NIR has routinely been used. However, in the case of diffuse reflectance NIR, the diffused and reflected depth of light in a tablet depends on several chemical and physical factors, such as the absorbance due to the chemicals, particle size, and bulk density. If the sample contains water, the depth decreases with increasing the amount of water due to the absorption. It is also known that the diffuse reflectance of light decreases with increasing the bulk density (Otsuka et al., 2007). On the other hand, high density tablet increases in transmission of light. Generally, it is considered that the depth is approximately 1 mm from the surface of tablet, hence not the appropriate tool to determine the amount of API present in the whole tablet. Transmission NIR can retrieve information from the whole tablet. Ito et al. and many other authors reported the determination of API content in a tablet using transmission NIR spectra (Alcalà et al., 2008; Gottfries et al., 1996; Meza et al., 2006). However, because of the low transmittance ratio, to calibrate the API quantity is strict on the tablet form such as thickness, bulk density, and the particle size.

Transmission Raman spectroscopy (TRS) is an alternative technique to determine API content in a tablet. Using TRS, partial least squares regression (PLSR) analysis was demonstrated to allow determination of the API content with high accuracy and precision (Griffen et al., 2016; Johansson et al., 2007; Matousek and Parker, 2006; Zhang and McGeorge, 2015). It was also documented that TRS had the ability to quantify the polymorphic forms of an API in intact tablets (Hargreaves et al., 2011; Zhang and McGeorge, 2015). Despite these previous reports, TRS remains under investigated for its utility in the determination of moisture content in a tablet primarily because Raman spectroscopy presents limitations in its inability to correct signals from water molecules. As a preliminary work to determine moisture content in a tablet using Raman spectroscopy, we focused on the determination of pseudo-polymorphic change hydrate and anhydrous of caffeine. In this study, the dehydration process of CAH was discussed by investigating the pseudo-polymorphic change. The crystalline change was investigated by calibrating the moisture contents in caffeine tablets via PLSR using both TRS and backscattering Raman spectroscopy (BRS).

2. Materials and methods

2.1. Materials

Caffeine hydrate (CAH) was purchased from Wako Pure Chemical Industries (Osaka, Japan). Its chemical structure is represented in Fig. 1. The bulk CAH powder was prepared under high relative humidity (RH%) condition of more than 95% for 4 days prior to use.

2.2. Thermal gravimetric analysis

The moisture content of CAH was determined using a thermogravimeter (TG) and differential thermal analysis (DTA) instrument (TG-8120, Rigaku, Tokyo, Japan). The measurements were performed using approximately 10 mg of CAH purging air with nitrogen gas and heated from 20 to 200 °C at a rate of 5 °C/min.

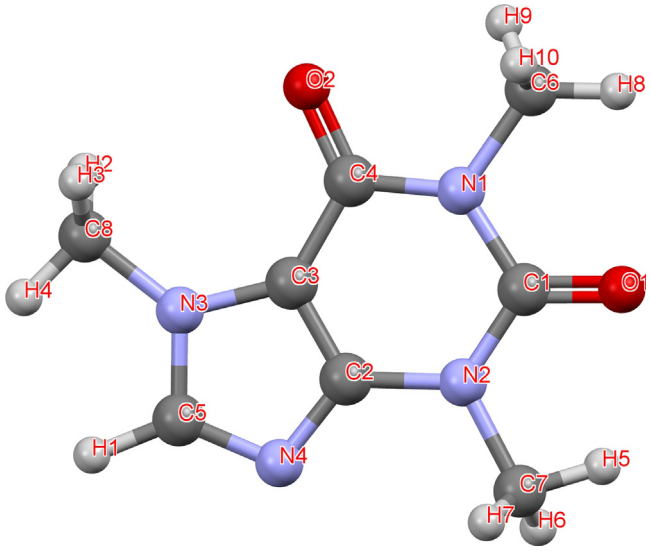

Fig. 1. Chemical structure of caffeine.

2.3. Tablet compression and dehydration

Tablets of various thicknesses and weights were prepared to monitor dehydration rates. The tablets were prepared using a hydraulic compression machine (HANDTAB-100, Ichihashi Seiki, Kyoto, Japan) with 8 mm in diameter of flat face punches and a die. The thickness was adjusted to 2.6 mm, 3.0 mm, 3.2 mm, 3.5 mm, and 4.0 mm, each associated with a defined amount of CAH set at 150 mg, 175 mg, 200 mg, 235 mg, 265 mg, respectively. The compression was performed under a constant pressure of 100 MPa. After the compression, the tablets were weighed out and were either left undried, or dried in an oven at 70 °C for 3 or 8 h. In total, 45 tablets were used for the measurements of moisture content and Raman spectroscopy.

The absolute moisture of the initial undried tablet (M_{init}) was obtained by TG measurement of the CAH powder, while that of the dried tablets (M_t) was determined at the drying time t, using the following equation where LOD represents the loss on drying:

$$M_t = M_{init} - \mathrm{LOD}. \quad (1)$$

2.4. Backscattering and transmission Raman spectroscopy

The BRS and TRS of the sample tablets were measured using a fiber-optic Raman probe connected spectrometer (Raman-HR-TEC, Stellarnet, Tampa, FL) and TRS100 (Cobalt Light Systems, Oxfordshire, UK), respectively. The BRS detector was an electronically-cooled InGaAs array detector, and a diode laser of 785 nm (Lab-LS-785, Innovative Photonic Solutions, Monmouth Junction, NJ) was used for excitation with an output laser power of 100 mW. The laser spot size of BRS was less than 0.5 mm in diameter. Spectral measurements were performed with 5 s of exposure time and integrated by 5 iterations.

The excitation laser of TRS was generated using a frequency stabilized diode laser operating at 830 nm. The laser spot size was 4 mm in diameter and the power at the sample was 650 mW (51.7 mW/mm^2). Samples were placed on an automated sample tray during the measurement. The spectral acquisition was performed with 0.3 s of exposure time and integrated by 3 iterations.