Real-Time Monitoring of Changes of Adsorbed and Crystalline Water Contents in Tablet Formulation Powder Containing Theophylline Anhydrate at Various Temperatures During Agitated Granulation by Near-Infrared Spectroscopy

MAKOTO OTSUKA, YOSHINORI KANAI, YUSUKE HATTORI

Research Institute of Pharmaceutical Sciences, Faculty of Pharmacy, Musashino University, Tokyo 202-8585, Japan

Received 11 February 2014; revised 17 April 2014; accepted 18 April 2014

Published online 15 May 2014 in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/jps.24006

ABSTRACT: Real-time monitoring of adsorbed water content (FW) and hydrate formation of theophylline anhydrate (THA) in tablet formulation during agitated granulation was investigated by near-infrared (NIR) spectroscopy. As the wet-granulation process of THA tablet formulation involves change in pseudo-polymorphs between THA and theophylline monohydrate (THM), the pharmaceutical properties of THA tablet depend on the degree of hydration during granulation. After mixing of the powder materials (4 g) containing THA, and excipients and the addition of 600 μL of binding water, the powder was kneaded at 27°C, 40°C, and 50°C and then dried. The mixing, granulating, and drying processes were monitored using NIR. The calibration models to predict THM and total water contents during granulation in THA tablet formulation were obtained by partial least-squares regression. The FW in the formulation was determined by subtracting THM from the water content. The results of the THA formulation powder bed during granulation by NIR monitoring indicated that the transformation pathway of the THA powder was THA ⇒ THM ⇒ THA at 27°C and 40°C, but that at 50°C was THA ⇒ THA ⇒ THA. The pharmaceutical properties, such as tablet porosity, hardness, tablet disintegration time, and dissolution rate of the final THA tablet products, were affected by the degree of crystalline transformation during granulation. © 2014 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 103:2924–2936, 2014

Keywords: theophylline anhydrate tablet formulation; chemometrics; crystal engineering; hydration; particle size; process analysis technology; real-time monitoring during agitated granulation; tablet hardness; dissolution test; temperature effect on pseudo-polymorphic transformation; chemometric near-infrared spectroscopy

INTRODUCTION

The pharmaceutical industry is highly regulated by official regulatory agencies, such as the US Food and Drug Administration (FDA), the European Medicines Agency, and the Pharmaceuticals and Medical Devices Agency, so final pharmaceutical products must meet very stringent specifications. Conventional pharmaceutical manufacturing is generally accomplished using processing batch tests, which are off-line, time-consuming, and less efficient laboratory tests conducted on randomly collected samples to evaluate quality. The production processes are not fully understood and are often inefficient black boxes. As information related to trouble in these processes is mainly obtained after production, it is difficult to perform process control.[1] To improve the quality of pharmaceutical products, the FDA's process analytical technology (PAT) initiative forms have been proposed as the basis of pharmaceutical Good Manufacturing Practice rules for the 21st century.[2] The guidelines for PAT recommend in-line, real-time analyses as a tool to monitor and control product quality during manufacturing process in the pharmaceutical industry. The ultimate goals of PAT are to open the black box system in manufacturing processes and to better understand the fundamental scientific mechanisms of manufacturing processes. Introduction of real-time analyses eliminates defective products, and increases manufacturing efficiency, as well as decreases the burden of finished product testing and ensures product quality throughout the industrial process.[3]

Using near-infrared (NIR) and Raman spectroscopy, spectra can be measured directly on intact samples without contact or sample destruction. In particular, NIR spectroscopy involving chemometrics is rapidly becoming an important technique for PAT in the pharmaceutical production process. Chemometrics,[4] such as multiple linear regression, principal component regression, and partial least-squares (PLS) regression, provides an ideal analytical method for extracting quantitative information about samples through any spectroscopic data on multicomponent samples in many industries.

Therefore, the NIR spectroscopic method involving chemometrics has been utilized to solve problems, such as uniformity of drug contents and polymorphic contents, particle sizes, and stability of bulk powders in pharmaceutical preparations.[5,6] The combination of NIR spectroscopy and chemometrics can be applied to quality control in the pharmaceutical industry.

Theophylline (TH) is a methylxanthine, and the most popular and important drug for treating mild-to-moderate persistent asthma in the form of generic drugs, with a long history.[7] Sustained-release TH is used to control inflammation in the airways in the lungs. Short-acting TH is used to control narrowing of the bronchial tubes, which may reduce asthma symptoms.[8] TH, which has several polymorphic forms,[9,10] and theophylline anhydrate (THA) and monohydrate (THM) crystalline forms,

Correspondence to: Makoto Otsuka (Telephone: +81-424-68-8658; Fax: +81-424-68-8658; E-mail: motsuka@musashino-u.ac.jp)

Journal of Pharmaceutical Sciences, Vol. 103, 2924–2936 (2014)

changes into THM at high relative humidity.[11] As THM was less soluble than THA,[9] the dissolution rate of THA decreased, dependent on the formation of hydrate. THA bulk powder in the pharmaceuticals was transformed into THM during storage and the wet granulation process, and the phase transformation of THA during processing affected the bioavailability of the products through their dissolution behaviors.[11–15] To obtain high-quality products, hydrate formation of THA during wet granulation with agitating and fluid bed granulators was studied quantitatively by in-line NIR and Raman methods and multivariate analysis as real-time analysis.[16–23] Wikström et al.[24] reported in-line monitoring of THA hydrate formation during high shear wet granulation using Raman spectroscopy. They investigated the effects of mixing speed and adding seed crystals on hydrate formation, and found that an increase in mixing speed shortened the onset time and increased the rate of crystalline transformation. The authors suggested that the transformation followed a simple solvent-mediated model. They[25] could also partly control the hydration process and the properties of their final products by adjusting the agitating speed and the kind of excipient. However, there are no reports on monitoring and controlling the pharmaceutical properties of granules without a change of the formulation during granulation.

In the present study, to control the quality of THA tablets, the raw granular materials were prepared at various granular temperatures, and then their pharmaceutical properties were monitored by nondestructive and noncontact measurement, an NIR spectroscopic method with chemometrics. It was found that the final tablet properties could be monitored and controlled by adjusting the granular temperature.

MATERIALS AND METHODS

Materials

Bulk drug powder (Lot: F22224) of THA was obtained from Shizuoka Coffin Company Ltd. (Shizuoka, Japan). The standard sample of THM was obtained by recrystallization from a saturated TH solution at room temperature after dissolving in hot distilled water, as reported previously.[11,15] The THA and THM powders were passed through a 200-mesh screen, and made up of particles less than 75 μm in diameter. The α-lactose monohydrate (LA; Pharmatose 200M; Lot No. 10466352) was obtained from DMV Fonterra Excipients (Vegjel Germany). Microcrystalline cellulose (MCC; CEOLUS PH101; Lot No. 18CB) was obtained from Asahikasei Chemicals Company (Tokyo, Japan) with an apparent density of 0.29 g/mL, and weight loss by drying of 2.0%–6.0%. Hydroxypropylcellulose (HPC; HPC-L; Lot No. NII-2611; molecular weight, 55,000–70,000 Da) was obtained from Nihon Soda Company Ltd. (Tokyo, Japan). The binder solution used was purified water obtained with an ultrapure water generator (Milli-Q; Millipore Company Ltd., Tokyo, Japan). All excipient powders were passed through a 42-mesh screen (355 μm in diameter) to reduce agglomeration before use. Known amounts of standard THM formulation samples containing 0%, 20%, 40%, 60%, 80%, and 100% THM were obtained by mixing THA and THM samples, and excipients with a mortar and pestle, as shown in Table 1. The standard THM formulation samples were measured by NIR for the establishment of the calibration model to predict THM content in the products.

Table 1. Chemical Components of Standard THM Formulation Samples to Evaluate THA Tablet Formulation

	THA (%)	THM (%)	LA (%)	MCC (%)	HPC (%)
THM-100	0.0	50.0	31.5	13.5	5.0
THM-80	10.0	40.0	31.5	13.5	5.0
THM-60	20.0	30.0	31.5	13.5	5.0
THM-40	30.0	20.0	31.5	13.5	5.0
THM-20	40.0	10.0	31.5	13.5	5.0
THM-0	50.0	0.0	31.5	13.5	5.0

Granulation Process

An ultrasmall-scale high-shear granulator (Type OW-1; Fox Science Company Ltd., Tokyo, Japan)[26,27] was used to prepare raw granules for the tablets. The granulator consisted of the containers (volume 20.0 mL, 2.90 cm in diameter) and a special triangular prism-shaped stirring rotor with a chopper made of Teflon, for which the environmental temperature could be controlled between 20°C and 70°C. The formulation powder blend (total 4.0 g) consisting of THA, 2.00 g; LA, 1.26 g; MCC, 0.54 g; and HPC, 0.20 g was mixed in the granulator at 500 rpm for 3 min. Next, 600 μL of purified water was added to the mixture at 60 μL/min using an automatic infusion pump (Type CR10; As One Company Ltd., Tokyo, Japan) during kneading for 10 min at 27 ± 1°C, 40 ± 1°C, and 50 ± 1°C, and then granulated for 44 min at the same temperature. After treatment, the obtained granules were dried at 70°C in an oven dryer for 24 h. The granulations were performed three times at various temperatures, and a total of 12 g of granules was obtained, then the granules and the compressed tablets were measured for their pharmaceutical properties.

Evaluation of Granule Size Distribution and Mean Particle Size

The granular particle size distribution after drying was measured by the sieving method as follows: six sieve screens (106, 150, 212, 355, 500, and 1700 μm; Testing Sieve; Tokyo Screen, Tokyo, Japan) were set up and used for particle size analysis. After the granule sample (4 g) was transferred to the preweighed sieve screens and shaken for 15 s by an electric vibrator, the mass fractions of granules were measured by weighing. The mean particle size was evaluated in terms of median diameter based on the cumulative weight profiles.

Measurement of Specific Surface Area

The specific surface area (Sw) was measured with a gas adsorption apparatus (one point method; Monosorb; Quantachrome Instruments, Boynton Beach, Florida) by using Brunauer–Emett–Teller (BET) gas adsorption. An adsorption gas containing 30% N_2 and 70% He was used at 15 mL/min for measurements. The sample weight was 500 mg. All values represent the average of three measurements.

Tablet Preparation

A compression/tension tester (Autograph; TG-50kN; Minebea Company, Ltd., Tokyo, Japan) with two load cells (upper and lower punches) and a displacement transducer were used to measure the upper and lower pressure and distance between the punches at 25°C. A punch of 8-mm diameter and die with flat surfaces were used to compress 200 mg of sample powder