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Application of the quantitative detection of a change in concentration of magnesium stearate in a feeder tube of tableting manufacture by real-time near-infrared spectroscopy

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Process analytical technology is important for the analysis and control of manufacturing processes. Near-infrared spectroscopy is widely used in various process analytical technologies for the analysis of the chemical componentsof solid dosage forms. Lubrication is an important process carried out before a tablet is produced. In this process, the concentration of lubricant, such as magnesium stearate (StMg), might change for one of many reasons during powder transport, which would be a critical problem such as variation in tablet compressibility and dissolution failure of compressed tablets. Our group investigated the feasibility of the quantitative monitoring of a change in the concentration of StMg in the feeder tube of tableting equipment employing real-time near-infrared spectroscopy.

1. Introduction

In pharmaceutical industry, there has been a drive in recent years to better understand products and to develop good manufacturing procedures employing innovative technology for the monitoring of processes. Since 2004, process analytical technology (PAT) has been an important issue in the analysis and control of manufacturing processes. PAT has appeared in the Technical Requirements for Registration of Pharmaceuticals for Human Use (Q8 to 11) of the International Conference on Harmonization (ICH) and the U.S. Food and Drug Administration (FDA) guidelines as an innovative framework (ICH Q8 2009; ICH Q9 2005; ICH Q10 2008; ICH Q11 2012;FDA Guidance for Industry 2004). The final goal of the PAT framework is a real-time risk assessment that is more scientific, robust, safeand reasonable than conventional approaches. The potential PAT framework would improve confidence in the implemented technology and its ability to portray process events accurately. The realization of PAT requires the detection of process behaviors on the basis of scientific understanding. It is desirable to observe the process behavior more frequently than a conventional approach does by employingan inline or online real-time monitoring sensor or analyzer. A wide range of PAT technologies employed for the analysis of chemical components in solid dosage forms use real-time near-infrared spectroscopy (NIRS) (Luypaert et al. 2007; Tok et al. 2008; Moes et al. 2006; De Beer et al. 2009; Lee et al. 2010; Burggraevea et al. 2013).

The tableting process includes the mixing of active substances and excipients *via* direct blending or granulation. A lubrication step employing a blender or mixer is then performed to ensure that the tablet blend does not stick to equipment. StMg is often used in this process. There is the possibility that such lubrication leads to critical problems such as variation in tablet compressibility and dissolution failure of compressed tablets through overlubrication or a change inthe concentration of the lubricant (Bolhuis et al. 1981; Mollan and Çelik 1996; Mehrotra et al. 2007). Real-time NIRS monitoring has been investigated for the component analysis of StMg to prevent homogenously and/or de-mixing during the blending process using a blender or mixer (Sekulic et al. 1996; Hagrasy et al. 2006; Nakagawa et al. 2013). Previous investigations of real-time NIRS monitoring have employed qualitative trend analysis. This approach detects and tracesthe behavior of StMg in the blending bin according to a changein spectrum behavior or calibration model. The approachhas been sufficient for the purpose of monitoring the blending process.

However, the lubrication process occurs before tableting during transfer of the raw material of the tablet to the tableting equipment. In the lubrication process, there might be a change in concentration of StMg due to segregation for one of many reasons during the powder transport. This may lead to critical problems such as variation in tablet compressibility and dissolution failure of compressed tablets. ICH and other guidelines suggest that a risk assessment is made to realize a process that is robust and safe.

Our group thus investigated the feasibility of the quantitative monitoring of changes in the concentration of StMg in the feeder tube before the tableting process employing real-time NIRS.

2. Investigations and results

2.1. Development of a partial least-squares regression (PLSR) calibration model of StMg for real-time NIRS

The model tablet in this study comprised theophylline as an active pharmaceutical ingredient; lactose, corn starch, and micro

Table 1: Proportions of the components of the formulation used in the investigation

Components	Target volume (mg/dose)	Percentage (wt %)
Teophiline	20.0	10.0
Lactose	98.0	49.0
Cornstarch	41.0	20.5
MCC	36.0	18.0
HPC-L	4.0	2.0
StMg	1.0	0.5
Amount	200.0	100.0

Table 2: Target concentration and the range of concentrations used to determine the calibration model of StMg

Weight of granule (mg/dose)	Weight of StMg (mg/dose)	Percentage of StMg (wt %)
199.0	0.5	0.25
199.0	0.6	0.30
199.0	0.7	0.35
199.0	0.8	0.40
199.0	0.9	0.45
199.0	1.0	0.50
199.0	1.1	0.55
199.0	1.2	0.60
199.0	1.3	0.65
199.0	1.4	0.70
199.0	1.5	0.75

cysteine cellulose as excipients; and StMg. The target concentration and the range of concentration for the calibration model of each component are given in Table 1. The target concentration of the active pharmaceutical ingredient was 20 mg/200 mg (10 wt%/dose) and that of StMg was 1 mg/200 mg (0.5 wt%/dose). The raw materials underwent granulation and lubrication was then conducted using the candidate components given in Table 2. The NIRS spectrum was acquired using a solid fiber probe at the powder directly. Multivariate analysis such as PLSR modeling can be conducted to quantitatively measure the concentration of StMg. Table 3 presents the calibration model obtained by PLSR modeling employing test-set validation, using the weighted percentage (wt%) based on the mass weighted resultas the reference method. The overall results of each calibration curve after test-set validation are shown in Fig. 1. The spectral range (7598 to 5326 cm^{-1}) and data pretreatment (second derivative and 25 smoothing points employing Savitky–Golay smoothing) used to calculate the PLSR model were decided inseveral preliminary investigations (Savitky and Golay 1964). The accuracy of the PLSR model was a root-mean-square of prediction (RMSEP) of 0.035% and R^2 of the validation set of 96.72%. To consider of specify to component, the first loading factor profile (loading 1) obtained from PLSR and the spectrum of each component after pretreatment are compared in Fig. 2. Each analysis gave similar profiles for StMg and loading 1, which were different from the profiles of other components. Consequently, this result provides evidence that the calibration model is specific for StMg.

2.2. *Real-time monitoring of StMg in the feeder tube of tableting equipment employing real-time NIRS*

Figure 3 is a schematic diagram of the probe setting of the monitoring system. The concentration of StMg in the raw material of the tablet was set to a target value of 0.5 wt%, and spectra were acquired for the powder flowing along the feeder tube. To determine the performance of the measurement system, the spectra recorded at the beginning and end of the experiment and the spectrum modeled for a StMg concentration of 0.5wt% are

Table 3: Standard errors, coefficient of determination (R2) and the number of factors for the PLSR calibration models evaluated

Calibration		Validation	
Dosage range (wt %)	0.25−0.75	Dosage range (wt %)	0.25−0.75
No. of spectra	39	No. of spectra	48
No. of PLS factor	4		
R^2(%)(*)	97.48	R^2(%)(*)	96.72
RMSEE(wt %)	0.023	RMSEP(wt %)	0.035

(*) Coefficient of determination
Data Pretreatment: Second derivative + 25 smoothing point Spectrum Range (cm^{-1}): 7598 to 5326 cm^{-1}

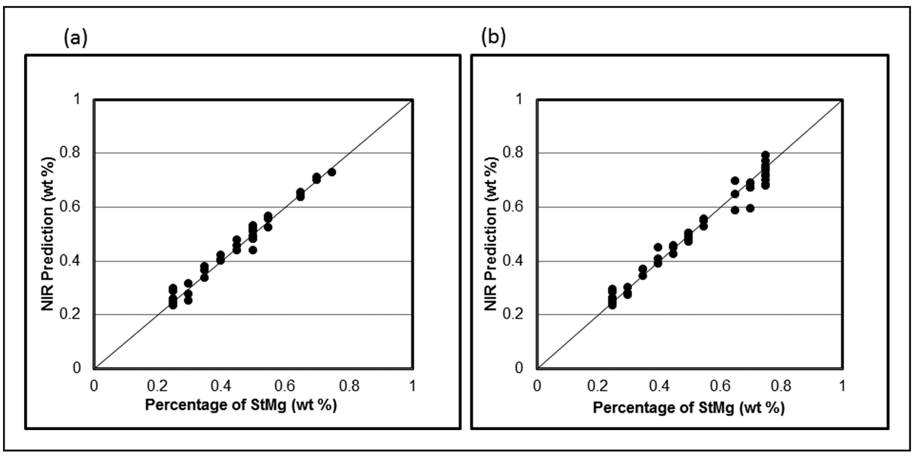

Fig. 1: Calibration model obtained by cross validation; the weighted volume of StMg (wt%) was used as a reference. (a) Calibration set, (b) Validation set.

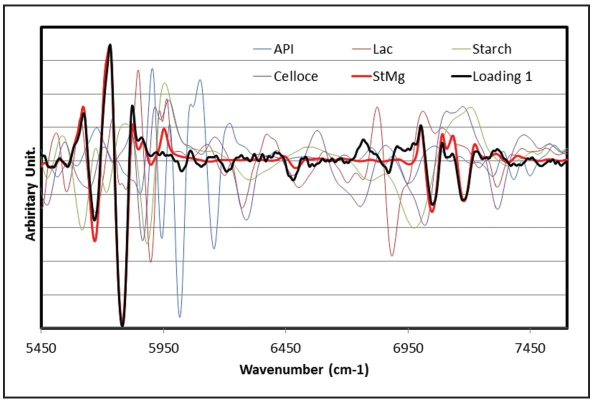

Fig. 2: Loading 1 of PLSR and the spectrum of each component. The profiles of Loading 1 and StMg are similar.

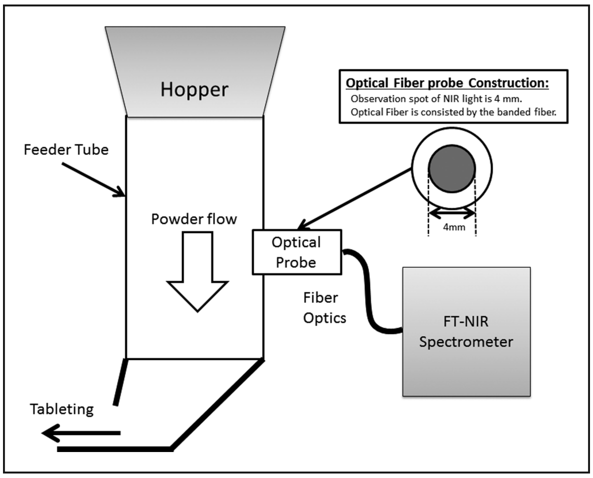

Fig. 3: Schematic diagram of the real-time monitoring system for StMg in the feeder tube.

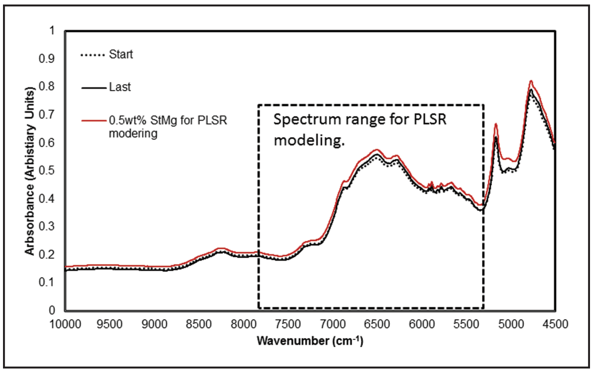

Fig. 4: Comparison of the spectra of powder in the feeder tube and the spectrum used for the PLSR model.

compared in Fig. 4. The qualities of spectra were sufficient for monitoring in range in the spectrum to use for the calibration model based on the fact that all of the spectrums did have similar the signal quality and noise level.

To reveal the prediction performance of the calibration model by monitoring the results for 500 s, time slices of the concentration of StMg predicted by spectrum acquisition in intervals of 5 s are shown in Fig. 4. The mean value of the prediction value was 0.51 wt% and the standard deviation was 0.027 wt%.

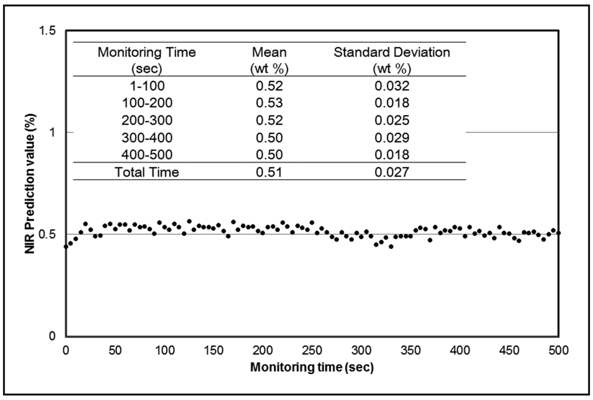

Fig. 5: Result of the real-time monitoring of StMg in the feeder tube of tableting equipment by real-time NIRS.

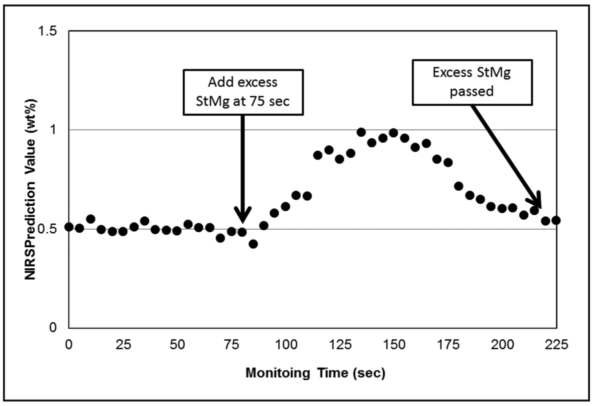

Fig. 6: Trial of error detection in terms of a change in the concentration of StMg detected by real-time NIRS.

2.3. Trial of concentration change detection of StMg by real-time NIRS

To test the feasibility of detecting process errors in terms of the StMg concentration, an excess amount of StMg was added to raw material powder. The powder was then deliberately added to the hopper at around 75 s in an experiment. The total monitoring time was 225 s. The results presented in Fig. 5 clearly show that it is possible to detect process error with a quick response in the case of StMg segregation.

3. Discussion

The present study investigated the quantitative monitoring of StMg in the raw material of a tablet in a feeder tube before tableting employing real-time NIRS. This investigation leads to the development of high-sensitivity calibration models that can be used to detect StMg quickly by employing quantitative multivariate analysis such as PLSR modeling of flowing powder. PLSR was conducted to create a high-performance calibration model by verified specify of StMg with the PLS loading data comparison. Observation of powder flowing along the feeder tube by real-time NIRS was shown to be sufficient to be evaluated. The qualities of spectra were sufficient for monitoring in the range in the spectrum to use for the calibration model based on the fact that all of the spectra did have similar signal quality and noise level. The prediction performance of the predicted values by the PLSR model verified for StMg monitoring did not exceed the RMSEP. A trial in which concentration fluctuation in the form of excess StMg was detected by real-time

NIRS demonstrated quick detection with time resolution of a few seconds.

Consequently, the present investigation clearly showed that changes of StMg could be detected at the feeder in the tableting process. The concentration of a lubricant like StMg in the feeder tube of the tableting process can change depending on formulation and process. Regulation guidelines such as those of the ICH and FDA suggest that a risk assessment should be made following a scientific approach. The approach proposed in this study can be used in such a risk assessment as discussed above.

4. Experimental

4.1. Acquisition of transmission near-infrared spectra

Spectra were recorded by a multipurpose analyzer that includeda Fourier-transform near-infrared spectrometer (Bruker Optick GmbH, Germany) and anoptical fiber probe for a solid sample. A thermoelectric cooling indium gallium arsenide (TE-InGaAs) internal detector was positioned within the equipment to detect the signal. The spectra were collected using Opus 6.0 software (Bruker Optick GmbH). Each spectrum was an average of 16 scans made at a resolution of 8 cm^{-1}, over the range from 10,000 to 4500 cm^{-1}. PLS calibration model development and test set validation were performed with the QUANT 2 module of the Opus 6.0 software (Bruker Optik Gmbh).

4.2. Sample preparation and testing

All samples were produced in a laboratory of Towa Pharmaceutical Company. Each concentration of blended powder used to obtain the calibration model was produced with the designed concentration of StMg. All monitoring experiments were conducted in the laboratory of Towa Pharmaceutical Company.

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