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Non-destructive prediction of enteric coating layer thickness and drug dissolution rate by near-infrared spectroscopy and X-ray computed tomography

Aoi Ariyasu, Yusuke Hattori, Makoto Otsuka*

Research Institute of Pharmaceutical Sciences, Musashino University, 1-1-20 Shinmachi, Nishi-Tokyo, Tokyo, 202-8585, Japan

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ABSTRACT

The coating layer thickness of enteric-coated tablets is a key factor that determines the drug dissolution rate from the tablet. Near-infrared spectroscopy (NIRS) enables non-destructive and quick measurement of the coating layer thickness, and thus allows the investigation of the relation between enteric coating layer thickness and drug dissolution rate. Two marketed products of aspirin enteric-coated tablets were used in this study, and the correlation between the predicted coating layer thickness and the obtained drug dissolution rate was investigated. Our results showed correlation for one product; the drug dissolution rate decreased with the increase in enteric coating layer thickness, whereas, there was no correlation for the other product. Additional examination of the distribution of coating layer thickness by X-ray computed tomography (CT) showed homogenous distribution of coating layer thickness for the former product, whereas the latter product exhibited heterogeneous distribution within the tablet, as well as inconsistent trend in the thickness distribution between the tablets. It was suggested that this heterogeneity and inconsistent trend in layer thickness distribution contributed to the absence of correlation between the layer thickness of the face and side regions of the tablets, which resulted in the loss of correlation between the coating layer thickness and drug dissolution rate. Therefore, the predictability of drug dissolution rate from enteric-coated tablets depended on the homogeneity of the coating layer thickness. In addition, the importance of micro analysis, X-ray CT in this study, was suggested even if the macro analysis, NIRS in this study, are finally applied for the measurement.

1. Introduction

The dissolution of orally administered drug products is a critical quality aspect, which can affect the bioavailability and pharmacokinetic (PK) profile, and finally the efficacy and safety of the drug products (Amidon et al., 1995). Many types of controlled-release drug products have been developed to obtain the expected *in-vivo* dissolution in the gastrointestinal tract and the desired PK profiles. Thus, it is essential to understand the dissolution behavior of the drug products and to control the factors that affect their dissolution properties, such as the thickness of the film coating layer.

Enteric-coated products represent one of the controlled-release products, which are intended to dissolve in the small intestine, not in the stomach. One commonly used enteric coating ingredient is pH-dependent polymers, which contain carboxylic acid groups. This coating remains undissolved in the low pH of the stomach and starts to dissolve slowly in the neutral pH of the small intestine. Thus, the pH-dependent dissolution property of the enteric-coated products depends on the solubility and pK_a of the drug and coating polymer, as well as the properties of the dissolution medium, such as pH and buffer capacity (Ozturk et al., 1988). Additionally, it depends on the composition and thickness of the enteric coating layer (Albanez et al., 2015).

Therefore, it is important for pharmaceutical manufacturing process to control the thickness of the enteric coating layer that determines the dissolution rate of the drug product to ensure a consistent product quality. There are many analytical techniques for investigation of the tablet surface, including the film coating layer. Microscopy, such as light microscopy and scanned electron microscopy (SEM), can be used to measure the layer thickness directly based on the expanded target image; however, cutting the target sample is necessary to expose the cross section of the coating layer, which leads to sample destruction. On the contrary,

* Corresponding author.
E-mail address: motsuka@musashino-u.ac.jp (M. Otsuka).

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spectroscopy, such as attenuated total reflection-Fourier transform infrared (ATR-FTIR), near-infrared (NIR) (Gendre et al., 2011b; Kirsch and Drennen, 1996; Möltgen et al., 2012), Raman (Kauffman et al., 2007; Romero-Torres et al., 2005), and terahertz spectroscopy (Zeitler, 2016), are non-destructive techniques. However, these techniques cannot directly measure the layer thickness, but can provide chemical quantitative information as absorption of light, from which the information of layer thickness can be derived depending on the optical path length. Correlation analysis between the obtained spectrum and the layer thickness allows the extraction of information and prediction of the layer thickness. NIR and Raman spectroscopy are often used as real-time monitoring techniques during the coating process because of their non-destructive nature and quick response (Moes et al., 2008; Müller et al., 2012; Pérez-Ramos et al., 2005). Furthermore, combination of spectroscopic and imaging techniques can provide more detailed information. Previous studies showed that the spatial distribution data of the coating layer thickness can be obtained by NIR chemical imaging (NIR-CI) (Maurer and Leuenberger, 2009; Möltgen et al., 2012) and terahertz pulsed imaging (TPI) (Ho et al., 2008; Müller et al., 2012; Niwa et al., 2014).

These non-destructive techniques enable direct comparison between the coating layer thickness and drug dissolution rate by predictive measurement of the layer thickness followed by measurement of the dissolution rate of the same tablet. It is generally known that the coating layer thickness of tablets or pellets correlates with the drug dissolution rate (Kirsch and Drennen, 1995; Satturwar et al., 2002). Gendre et al. showed the correlation for the sustained release tablet and predicted the dissolution rate using NIRS (Gendre et al., 2011a). This relation is also critical for enteric-coated tablets because of their thick coating layer and slow dissolution rate, however, only a few researchers studied this relationship (Spencer et al., 2008).

In this study, the correlation between enteric coating layer thickness and drug dissolution rate was investigated using two commercial aspirin enteric-coated tablets. In addition to NIRS, X-ray CT technique was adopted for non-destructive measurement of the coating layer thickness distribution. X-ray CT is a relatively new but a very strong tool for noninvasive investigation of the internal three-dimensional (3D) structures of various objects. It has been applied for monitoring of the dynamic changes inside tablets during the dissolution process (Li et al., 2012; Otsuka et al., 2009) and evaluation of the coating layer thickness of particles (Perfetti et al., 2010; Sondej et al., 2015).

2. Materials and methods

2.1. Materials

2.1.1. Materials

Two commercial enteric-coated aspirin 100 mg tablets were used, which were coded as product A and B. The diameter was approximately 7 mm and the average weight was approximately 137 mg for both tablets. Aspirin core tablets of both products were prepared by removing the enteric coating layer.

The major components were acetylsalicylic acid (aspirin) and crystalline cellulose for aspirin core tablets, and methacrylic acid copolymer LD (L30D-55) and talc for enteric coating layer based on the information on the product documents.

To obtain reference NIR spectra of pure materials, aspirin, methacrylic acid copolymer LD (L30D-55), and talc were purchased from Nichi-iko pharmaceuticals (Toyama, Japan), Evonik industries (Essen, Germany), and Hayashi Chemicals (Tokyo, Japan), respectively.

2.1.2. Preparation of dissolution medium

For the dissolution tests, the 2nd fluid for dissolution test (pH 6.8) provided in the Japanese Pharmacopoeia 17th edition (JP17) was used, which was specified as the dissolution medium for release testing of many commercial aspirin tablets.

2.2. Methods

2.2.1. NIR measurement

A Fourier transform near-infrared (FT-NIR) spectroscopy apparatus (MPA, Bruker, Ettlingen, Germany) was used for surface measurement of the tablets. The scanning range was 12,500–4000 cm^{-1}, resolution was 8 cm^{-1}, and scan integration number was 32. Using diffuse reflectance mode with an integration sphere, the NIR spectra of the tablet surface were obtained for both sides of each tablet as shown in Fig. 1.

2.2.2. Measurement of enteric coating layer thickness

After NIR measurements, the tablet was cut vertically as shown in Fig. 1, and the cross section was observed using a digital microscope (VHX-100, Keyence, Osaka, Japan) attached with a zoom lens (VH-Z35, Keyence, Osaka, Japan) under low magnification of ×35. According to the outer coating layer of the cross section, the coating layer thickness at the tablet face and side regions was measured at more than 30 points at constant intervals.

The average coating layer thickness per each side of the tablet face was calculated using the thickness values at more than nine points, and represented the dependent variable for preparation of the NIRS-based calibration model.

2.2.3. Development of a calibration model for coating layer thickness

For development of a calibration model using partial least squares (PLS) regression, OPUS 6.5 software (Bruker, Germany) was applied. For each product, data sets of 41 pairs of the NIR spectra and the corresponding enteric coating layer thickness values were prepared for PLS regression. The data sets included 40 pairs for each side of the 20 tablets and one pair of the NIR spectrum of aspirin core tablet without the coating layer. Test set validation method was applied for the calibration model using 20 data pairs from 10 tablets as “Test” samples, and 21 pairs from the other 11 tablets including one pair of aspirin core tablet as “Calibration” samples.

2.2.4. Dissolution test

A dissolution test apparatus (NTR-6100A, Toyama Sangyo, Osaka, Japan) was used for the dissolution tests according to the paddle method described in JP17 using a rotation speed of 75 rpm. The test solution of 5 mL was sampled from each vessel at each time point, filtered through a 0.45-μm membrane filter and the drug concentration was determined by high-performance liquid chromatography (HPLC) analysis.

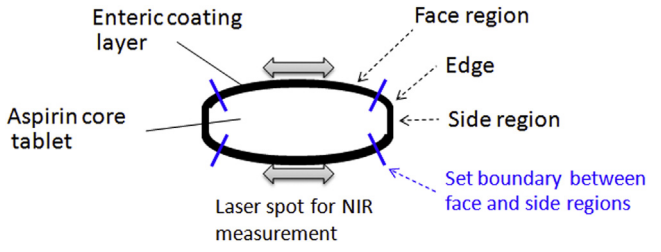

Fig. 1. Illustration of the cross-section of aspirin enteric coated tablets. The area measured by NIRS is presented by the arrow. The boundary is also presented which was set at 0.5 mm inside from the tablet edge to separate between the face and side regions for analysis of the coating layer thickness distribution.