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Investigation of film thickness uniformity on tablets by handheld Raman spectrometer

Srisakul Srisuk, Jittima Chatchawalsaisin

Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmaceutical Sciences, Chulalongkorn University, Bangkok 10330, Thailand

Corresponding Author:
Jittima Chatchawalsaisin, Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmaceutical Sciences, Chulalongkorn University, Bangkok, Thailand.
Tel.: +66(0)2-218-8274.
E-mail: jittima.c@chula.ac.th

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ABSTRACT

Purpose: The aim of this study was to investigate the uniformity of film thickness on coated tablets using handheld Raman spectrometer. **Methods:** Oval-shaped tablets were coated with Opadry® II blue at a pan speed of 8 rpm and spray rates of 8.2 and 10.5 g/min. The coating process was also carried out at the pan speed of 14 rpm and spray rate of 8.2 g/min. Other process parameters, that is, inlet air temperature and atomizing air pressure were kept constant. Twenty coated tablets were taken at 10 min intervals for determination of weight gain. The film deposited on both faces and the band of three tablets was examined by handheld Raman spectrometer. Surface morphology was investigated by scanning electron microscope. **Results:** The results showed that the coating process could provide smooth film coating on the tablets. An increase in the intensity of specific Raman peaks of TiO_2 in the film corresponded to the weight gain. Average and standard deviation of the intensity of the Raman peaks indicated that the tablet faces had thicker and more uniform film than the band region. **Conclusion:** This work demonstrated feasibility of handheld Raman spectrometer as a potential tool for measurement of film thickness uniformity on tablets.

Keywords: Film coating, film thickness uniformity, handheld Raman spectrometer, pan speed, spray rate

INTRODUCTION

Film coating process is commonly employed in manufacturing pharmaceutical solid dosage forms such as granules and tablets for several purposes. Non-functional films are applied to ease identification, mask the taste, or serve as protective barrier to prevent drug degradation caused by environmental factors. Functional films are used for modification of drug release, including protecting the acid-labile drug from degradation in stomach, targeting the drug release to a specific site, or providing drug controlled release.[1] Thus, one critical quality attribute of the coated dosage form is desired film thickness as it is associated with performance including stability and drug release characteristics of the coated products.

In general, coating conditions can impact on film quality and thickness uniformity. Pan speed and total coating time are critical process parameters having direct impact on film thickness. Both parameters facilitate distribution of coating liquid and are involved with dwell time and the number of times for the tablet passing spray zone in the coating pan. Other process parameters, such as nozzle-to-bed distance, spray rate, atomizing air pressure, as well as inlet air temperature and flow rate should be properly set up to avoid coating defects.[2,3] These parameters are critical to droplet size of atomized coating liquid reaching tablet surface, solvent evaporation, and hence film formation. Relatively small droplets and/or too high evaporation rate potentially cause spray drying of coating liquid, resulting rough surface. While, larger droplets and/or low evaporation rate can cause over-wetted surface, resulting in sticking and picking. The coating defects ultimately cause variability of film thickness. In addition, the shape of core tablets is an important variable influencing on degree of mixing in a pan coating process. The tablet shape which deviates from spherical or circular biconvex, such as oval or capsule, usually provides relatively poor mixing and coating uniformity.[4,5] The coating process of these shapes should be more tightly monitored and controlled to ensure final product quality.

Desired film thickness which is commonly referred to weight gain on the coated tablets can be consistently achieved under optimal process parameters. However, weight gain does not give information about uniformity of the film thickness. In practice, it is more likely that film coating is unequally distributed over the tablet surface. The film thickness variability on the coated tablets can be determined by scanning

electron microscopy.[6] However, it is a destructive technique and difficult to apply as in- and on-line process monitoring and control. Non-destructive techniques have been developed as a part of Process Analytical Technology framework which is intended to facilitate process understanding and control the manufacturing process though real time measurements of critical quality attributes of raw and in-process materials.[7] Many non-destructive tools, such as NIR spectroscopy,[8] Raman spectroscopy,[9-12] image analysis,[13] and terahertz pulsed imaging[14] have been introduced to monitor and control coating process. Among these techniques, Raman spectroscopy is a widely used technique. An application of Raman spectroscopy as tool for monitoring tablet coating process began in 2005 by Romero-Torres *et al*.[9] who demonstrated correlation between Raman spectra to the tablet coating times by partial least squares regression. The intensity of Raman spectra, which were associated with the coating polymer, increased proportionally to the coating time. Strong correlation between the Raman spectra and the weight gain was found when TiO_2 was present as opacifier in film coatings.[10-12] Recently, handheld Raman spectroscopy has been also introduced to pharmaceutical applications, such as drug identification[15] and counterfeit drug detection.[16] It is easy to use by non-specialists and portable. While, some limitations, for example, large laser beam, large laser energy, relatively narrow scanning range, as well as difficulty in focusing are demonstrated.[17,18] So far, the use of handheld Raman spectrometer for film coating process monitoring has not yet reported. The aim of this study was to investigate the ability of handheld Raman spectroscopy for monitoring film thickness uniformity during coating process, with different pan speeds and spray rates. The oval-shaped tablets which were likely to demonstrate poor mixing in the coating pan were used as cores.

MATERIALS AND METHODS

Film Coating Process

Film coating was carried out in a 15 inch perforated coating pan (Thai coater®, Bangkok, Thailand). 1.5 kg of oval-shaped tablets debossed with letters on one face of antiviral drugs (Government Pharmaceutical Organization, Bangkok, Thailand) were used as cores and Opadry®II blue containing lactose monohydrate, hypromellose, TiO_2, triacetin, and FD&C blue (Colorcon, Shanghai, China) was used as coating liquid. The core tablets were warmed up in the coating pan to temperature of 40 ± 1°C, at the inlet temperature at 80°C. Then, coating process was operated with different pan speeds and varied spray rates of coating liquid, as shown in Table 1. The inlet air temperature (80°C) and atomizing air pressure (3 bar) remained constant over coating time. During the process, 20 tablets were taken randomly from different locations inside the coating pan every 10 min up to 90 min. The product temperature was monitored by infrared thermometer (IR50i, Irtek, WA, Australia) at about 1 min before sampling.

Surface Morphology

The samples taken at the end of process (90 min) were coated with gold and then examined using Scanning Electron Microscope (SEM, JEOL JSM-IT300, JEOL Ltd., Tokyo, JAPAN).

Table 1: Coating process parameters

Process	Inlet air temperature (°C)	Atomizing air pressure (bar)	Pan speed (rpm)	Spray rate (g/min)
A	80	3	8	8.2
B	80	3	8	10.5
C	80	3	14	8.2

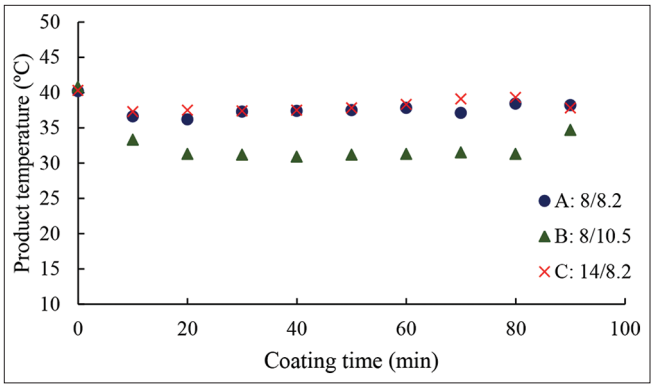

Figure 1: Product temperature monitored during coating process A, B, and C

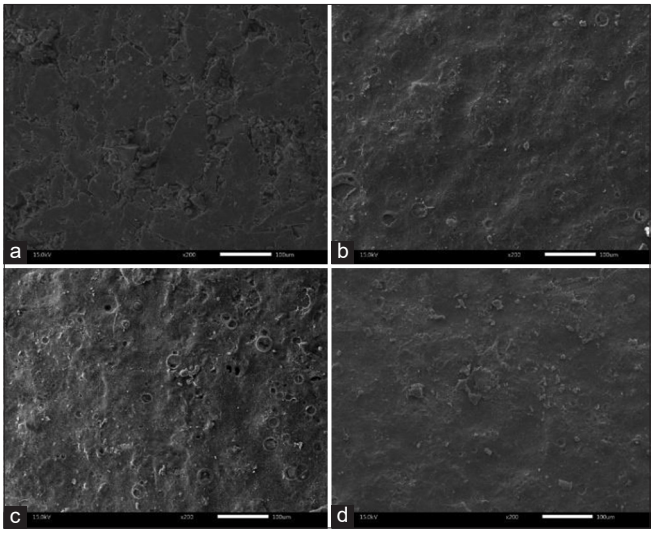

Figure 2: SEM images of (a) core tablet and coated tablets at the end of coating, (b) process A using pan speed of 8 rpm and spray rate of 8.2 g/min, (c) process B using pan speed of 8 rpm and spray rate of 10.5 g/min, and (d) process C using pan speed of 14 rpm and spray rate of 8.2 g/min

Weight Gain

Twenty tablets collected from three different locations inside the coating pan were weighed on a 5-digit balance (XP205, Mettler-Toledo AG, Greifensee, Switzerland). The weight gain was calculated using the following equation:

$$\%weight\ \ gain = \frac{W_t - W_0}{W_0} \times 100$$

where, W_0 and W_t are the weight of core tablets and of coated tablets taken at each time point, respectively.

Raman Spectroscopy

The film deposited on the sample of three tablets which were taken from three different locations inside the coating pan was examined by handheld Raman spectrometer (Rigaku Analytical Devices Inc., Wilmington, USA) using laser power of 450 nm, measurement time of 1.5 s, with 16 scans. For each tablet, 14 different points (three points positioned on each tablet face and total of eight points positioned on the tablet band) were measured. The average and standard deviation (SD) of intensity of the characteristic Raman peak were calculated separately for the debossed face (L), non-debossed face (NL) and band (B) of coated tablets. The average represents the film thickness on the tablet faces and the tablet band of an individual tablet; and the SD represents the variability of the film thickness on the face regions and the band region. The grand average represents film thickness all over the coated tablets.

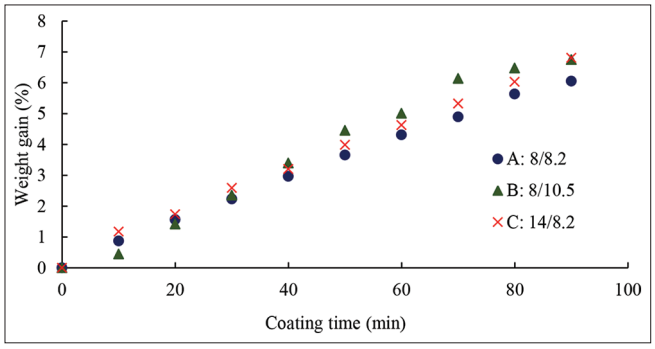

Figure 3: Cumulative weight gain as a function of coating time

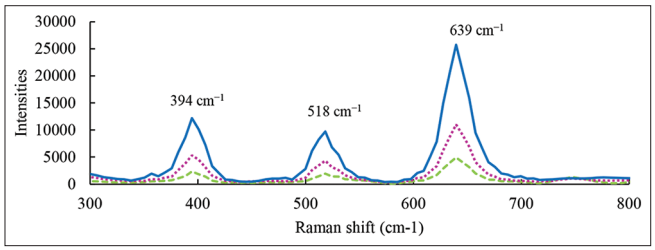

Figure 4: Raman spectra of film coatings at 10 min (green), 40 min (pink), and 90 min (blue) of process C

RESULTS AND DISCUSSION

Coating process parameters employed in the present study provided stable process over 90 min as shown by consistent product temperature [Figure 1]. The product temperature was influenced by spray rate of coating liquid. The low spray rate, that is, 8.2 g/min of process A and C caused higher product temperature.

Overall, tablets were successfully coated as shown by no defect on film coatings. On a microscopic level, SEM images reveal. SEM images reveal the surface morphology of core tablet [Figure 2a], comparing with that of coated tablets. Process A and C gave relatively smooth film [Figure 2b-d]. Balance between the coating liquid spray rate and the inlet temperature allowed sufficient time for spray droplet to spread, coalesce and dry, and giving smooth surface of the coated tablets. The relatively low spray rate in aqueous film coating process was previously reported as one of process parameters providing smooth and homogenous film coatings.[19] Furthermore, increasing pan speed resulted in a more coating uniformity was found,[4] but this effect was not clearly observed for the two pan speeds studied.

The weight gain increased almost linearly with time [Figure 3], indicating the progress of film deposition on the tablet surface over the coating time. With the relative high liquid spray rate of process B or high pan speed of process C, the film was likely to be thicker. The Raman spectra also changed with time. The characteristic peaks at 394, 518, and 639 cm^{-1} of TiO_2[20] were markedly determined in the Raman spectra. An increase in the intensity of Raman peaks with increasing coating time was observed [Figure 4]. As all the characteristic peaks responded to the weight gain in similar manner (data not shown), the Raman peak at 639 cm^{-1} resulted from examination the film coating of process C is an example used for discussed for thickness and intra-tablet uniformity of film coatings.

Correlation between the grand average intensity of the Raman peak and the weight gain as a function of time is demonstrated as in Figure 5. This indicates that thickness of coating layer on tablets can be measured by handheld Raman spectrometer.

It can be seen that the variability of film thickness on the two faces and the band of tablet was small during early period of coating process up to 30 min. Beyond that period, the film

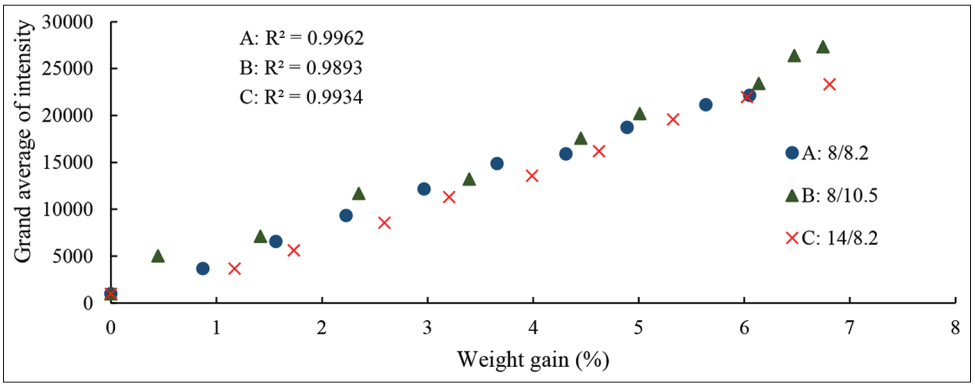

Figure 5: Correlation between the grand average intensity of the Raman peak at 639 cm^{-1} and the weight gain

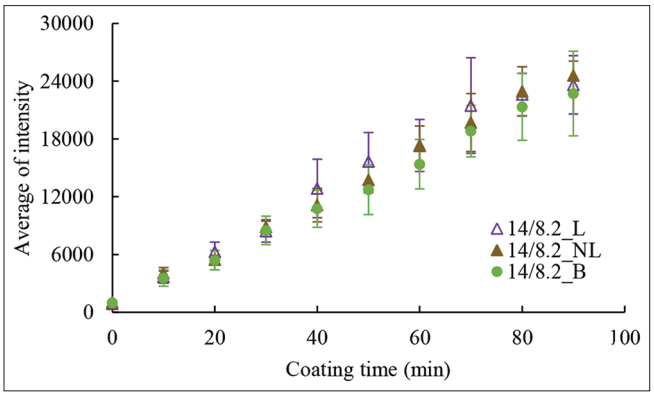

Figure 6: Average of the intensity (± SD) of Raman peak at 639 cm^{-1} against the coating time of process C. L, debossed face; NL, non-debossed face; and B, band

on the tablet faces was thicker than the band. The result agrees with that from the previous experiment and the combined discrete element method-Monte Carlo simulation algorithm and NIR techniques.[5,21] The film thickness variability is involved with preferred tablet orientation when passing spray zone. The flat orientation is more likely to pass spray zone.[4,5] The variability of film thickness on the band (B) was increased over the coating time as evidenced by higher SD [Figure 6]. The film thickness over the L face also had higher variability, comparing with the film thickness over the NL face, probably due to that determination of thicker film in the region of debossed letters where more coating material deposited. With the present process parameters, longer coating time could not improve the film thickness uniformity which is in consistent with simulation results.[5]

CONCLUSION

This study demonstrates feasibility of using handheld Raman spectrometer as a non-destructive tool to monitor film thickness uniformity on oval-shaped tablets, debossed with letters on one face during coating process. The average and SD values of Raman peak intensity of marker material, that is, titanium dioxide in the film coating are the key measures of film thickness uniformity.

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