Monitoring Tablet Surface Roughness During the Film Coating Process

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ABSTRACT

The purpose of this study was to evaluate the change of surface roughness and the development of the film during the film coating process using laser profilometer roughness measurements, SEM imaging, and energy dispersive X-ray (EDX) analysis. Surface roughness and texture changes developing during the process of film coating tablets were studied by noncontact laser profilometry and scanning electron microscopy (SEM). An EDX analysis was used to monitor the magnesium stearate and titanium dioxide of the tablets. The tablet cores were film coated with aqueous hydroxypropyl methylcellulose, and the film coating was performed using an instrumented pilot-scale side-vented drum coater. The SEM images of the film-coated tablets showed that within the first 30 minutes, the surface of the tablet cores was completely covered with a thin film. The magnesium signal that was monitored by SEM-EDX disappeared after ~15 to 30 minutes, indicating that the tablet surface was homogeneously covered with film coating. The surface roughness started to increase from the beginning of the coating process, and the increase in the roughness broke off after 30 minutes of spraying. The results clearly showed that the surface roughness of the tablets increased until the film coating covered the whole surface area of the tablets, corresponding to a coating time period of 15 to 30 minutes (from the beginning of the spraying phase). Thereafter, the film only became thicker. The methods used in this study were applicable in the visualization of the changes caused by the film coating on the tablet surfaces.

KEYWORDS: tablet coating, surface roughness, laser profilometer, scanning electron microscopy (SEM), energy dispersive X-ray (EDX).

INTRODUCTION

Surface roughness is an important parameter in pharmaceutical tablet dosage forms. Surface roughness has been shown to have an influence on or to reflect the changes in many process variables, such as choice of excipients and compression pressure, that affect the final quality of the product. The surface roughness of uncoated tablets plays an important role in dissolution, friability, and adhesion of sugar coatings and polymer film coatings.[1-6] In addition, the surface roughness of film-coated tablets has been connected to dissolution rate, permeability, and gloss.[7,8]

Monitoring, controlling, and understanding pharmaceutical processes have become increasingly important since the adoption of the US Food and Drug Administration process analytical technology (PAT) guidance.[9] The laser profilometer is a promising tool in process control, product quality assessment, and stability since it gives quantitative information about surface roughness.[10] The laser profilometer has been successfully used in off-line monitoring of the film coating process.[11] To date, the most widely used approach in monitoring the film coating process and quantifying film thickness has been near-infrared (NIR) spectroscopy.[12,13] NIR spectroscopy is based on diffuse reflectance, so the surface roughness affects the detected signal.[14]

Additionally, scanning electron microscopy (SEM) and energy dispersive X-ray (EDX) analysis have been used in pharmaceutics to identify different elements in dosage forms and excipients.[15,16] The amount of magnesium stearate has been previously studied with EDX analysis of the surface of powder particles.[17] The distribution of titanium dioxide pigment has also been studied (eg, in paints).[18]

The aim of this study was to evaluate the change of surface roughness and the development of film coating during the film coating process using laser profilometer roughness measurements, SEM imaging, and EDX analysis.

MATERIALS AND METHODS

Materials

The following materials were used for preparing tablet cores: theophylline anhydrate (PhEur), microcrystalline cellulose (Avicel PH-102, FMC International, Little Island, Cork, Ireland), talc (PhEur), and magnesium stearate (PhEur). The aqueous film coating solutions contained hydroxypropyl methylcellulose (HPMC; Methocel E5, Dow Chemical,

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Midland, MI), polyethylene glycol (Macrogolum 400, Fluka Chemie, Buchs, Switzerland), titanium dioxide (PhEur), and purified water (PhEur).

Preparation of Tablet Cores and Coating Solution

The composition of the tablet cores was as follows: theophylline anhydrate 5% (wt/wt), microcrystalline cellulose 86% (wt/wt), talc 8% (wt/wt), and magnesium stearate 1% (wt/wt). The tablets were compressed in a rotating tablet machine (Kilian and Co, GmbH, Köln, Germany) to a constant breaking strength of 95 to 100 N using 11-mm biconcave punches. The average weight of the tablets was 500 mg, and the friability was 0.6%.

The 2 coating liquids were as follows: (1) HPMC 8% (wt/wt), polyethylene glycol 1.6% (wt/wt), and purified water 90.4% (wt/wt); and (2) HPMC 8% (wt/wt), polyethylene glycol 1.6% (wt/wt), titanium dioxide 2.4% (wt/wt), and purified water 88% (wt/wt). To prepare the coating solution and pigmented dispersion, half of the calculated amount of water was heated (80-90°C), and the polymer was added to the hot water under magnetic stirring. After the polymer had been dispersed, the remaining cold water was added. When all the polymer was dissolved, plasticizer and pigment were added to obtain a total of 1000 g of coating liquid.

Film Coating of Tablets

The tablets were film coated in a laboratory-scale instrumented side-vented drum-coating apparatus (Thai coater, model 15, Pharmaceuticals and Medical Supply Ltd Partnership, Bangkok, Thailand). Each coating batch comprised 1.0 kg tablet cores. In the film coating experiments, the conditions of user-controllable process parameters were adjusted as follows: pump speed (flow rate) 2.8 rpm, pneumatic spraying pressure 300 kPa, drum air temperature 40°C, rotating speed of the drum 7.0 rpm, negative air pressure (drum) 5.0 Pa, and outlet air flow rate 20 L/s. The tablets were preheated for 5 minutes until the drum temperature was 40°C, and the rotating speed of the drum was adjusted to 3.0 rpm for the preheating and postdrying steps. After being sprayed, the tablets were dried for 5 minutes at 40°C in the drum coater. Thereafter, the film-coated tablets were kept at a controlled room temperature (25°C/relative humidity 60%) for at least 24 hours until they were studied. The thickness of the coating (35-40 μm) was estimated from the increase of the tablet height (n = 10), which was measured with a digital micrometer (Sony Micrometer, Sony Magnescale Inc, Tokyo, Japan). For laser profilometry, multiple samples of the film-coated tablets (n = 20-30) were taken immediately prior to film coating (spraying phase) and subsequently at 2.5, 5, 10, 15, 20, 30, and 45 minutes.

Surface Characterization

SEM

The surface of the film-coated tablets was studied by SEM (Zeiss DSM 962, Carl Zeiss, Oberkochen, Germany). The preparation of the sample was accomplished by placing the tablet onto a specimen holder. The samples were coated with a gold-palladium target using a vacuum evaporator. SEM images were obtained at an acceleration voltage of 8 to 10 kV. EDX analysis as an extension of SEM (Oxford Isis EDS-detector, Oxford Instruments Ltd, High Wycombe, UK) was used to detect the magnesium stearate and titanium dioxide of the tablets. EDX analysis was used in the mode of semiquantitative detection, and the acceleration voltage used was 20 kV.

Laser Profilometry

Tablet surface roughness was measured with a laser profilometer (UBM Microfocus Measurement System, UBM Messtechnik GmbH, Ettlingen, Germany). Tablet surface roughness (n = 6) was studied using an area of 3 mm × 3 mm and a resolution of 125 points/mm. The resolution in the vertical direction was ±0.1 μm, and the measurement time for each tablet was 30 minutes. The laser output was 0.2 mW and the laser wavelength 780 nm. The reflectance signal from the laser profilometer was recorded at the same time as the roughness information. The maximum reflectance of 100% corresponds to a mirror surface, and 5% is the minimum reliable reflectance of which measurement can be made. The tablet core surfaces and the final coated tablet surfaces were also measured with a higher resolution of 1000 points/mm, to image the 3D shape of the surface. The average roughness values (Ra) were determined from at least 6 tablets. After data collection, the image data were leveled using a data-analysis program (Ubsoft version 2.8 DOS, UBM Messtechnik GmbH) to remove roundness caused by roundness of the tablet. Laser profilometer images showing the 3D shape of the surface were drawn by the Mathematica 4.0 program (Wolfram Research Inc, Champaign, IL). The differences in the results were analyzed using Student t test in Microsoft Excel software (Microsoft Excel 2002, Microsoft Corporation, WA).

Roughness Parameters

The average roughness (Ra) parameter used in this study was calculated from the height data according to Equation 1:

$$Ra = \frac{\sum_{n=1}^{N} |Z_n - Z^-|}{N} \quad (1)$$

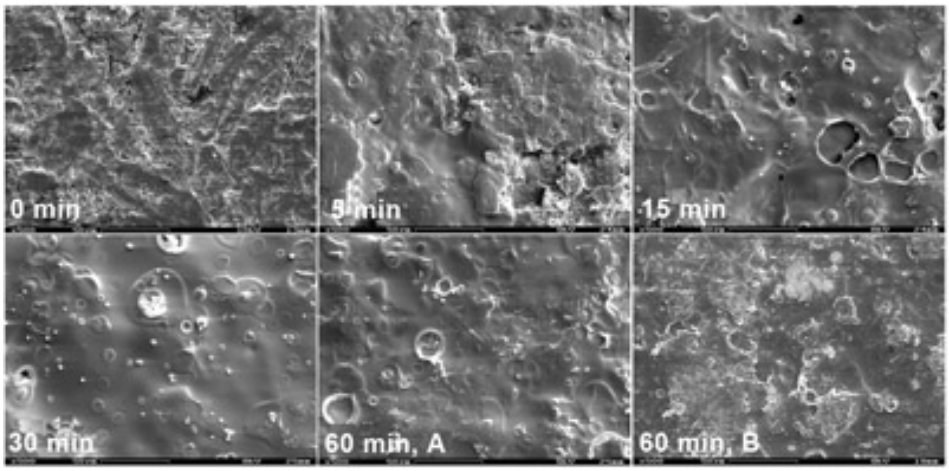

Figure 1. Scanning electron micrographs showing the progress of film coating of tablets in a side-vented drum coater: 0 minutes (surface of the tablet core); 5 minutes (batch 1); 15 minutes (batch 1); 30 minutes (batch 1); 60 minutes, A (final unpigmented film-coated tablet, batch 1); and 60 minutes, B (final pigmented film-coated tablet, batch 2).

where Z_n was the individual height value of 1 measurement point and $\bar{Z}$ the mean value of all the height data points. N was the number of measurement points.

Results and Discussion

Visual Appearance of Surface

On the tablet core surface (Figure 1), particles of microcrystalline cellulose were easily seen (long particles). The surface had flat areas, and there were deep holes between larger particles. These areas were also visible in laser profilometer images (Figure 2a). When the spraying of batch 1 had lasted 2.5 minutes, some slight modification and coating of the surface could be seen, but the surface was nearly the same as that of the core tablet (Figure 1). After 5 minutes of coating there were areas on the tablet surface that had coating, but most of the surface had the appearance of the core tablet (Figure 1). After 15 minutes the surface had been covered with a thin layer of coating and only larger holes from the tablet core were visible under the coating (Figure 1). After 30 minutes the coated surface had not changed markedly from its appearance at 15 minutes (Figure 1). The development of the coating was fairly similar for batch 2 (with titanium dioxide) and batch 1, but there were small particles visible in the coating in batch 2 at 60 minutes that were not visible for batch 1 at 60 minutes (Figure 1). These particles were most likely titanium dioxide aggregates. The laser profilometer images from the coated tablets look quite different for batch 1 and batch 2 (Figures 2b and 2c). In batch 1, tablets without titanium dioxide, the surface was rougher and looked more porous (Figure 2b). The tablet from batch 2 had a slightly smoother appearance (Figure 2c) because the titanium dioxide made the batch 2 coating have better reflection properties. The reflectance signals recorded at the same time as the roughness measurements showed that batch 2 had clearly better reflection properties than batch 1 or the core tablets (Figure 3). The core tablets had a reflectance of 19%, which was higher than the reflectance of the batch 1 tablets. During the film coating process the amount of reflectance changed differently in batch 1 and batch 2. In batch 1 the reflectance started to decrease right from the beginning and continued decreasing for

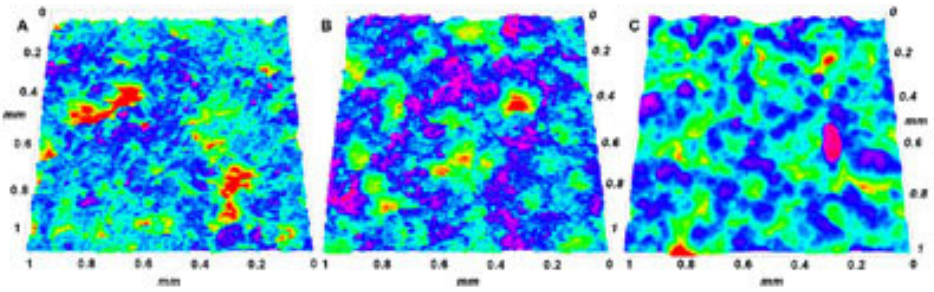

Figure 2. Laser profilometer 3D images showing texture and roughness of the film coating of tablets (final products): (A) tablet core, Ra 1.86 μm; (B) unpigmented film-coated tablet (batch 1), Ra 4.38 μm; and (C) pigmented film-coated tablet (batch 2), Ra 2.96 μm. Ra indicates average roughness.

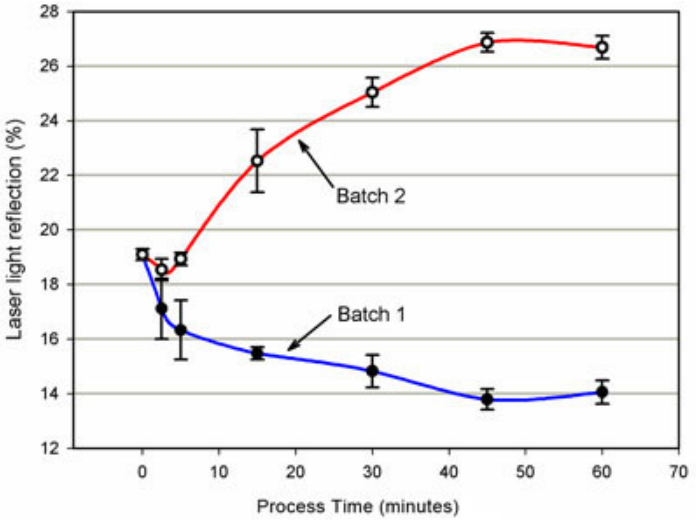

Figure 3. Laser profilometer reflection signals as a function of process time. The graphs show the change of laser light reflection of the tablets in batch 1 and batch 2.

45 minutes. After 45 minutes of spraying time the reflectance was still at the same level. In batch 2 the reflectance did not change at the beginning but then rose for 45 minutes, at which point it peaked. Laser profilometer reflectance information has previously been used to give qualitative information about surface properties of tablets and about surfaces where pigments have been used.[19,20]

Monitoring the Inorganic Elements During Coating

EDX analysis of tablet cores clearly showed a magnesium peak that came from the magnesium stearate of the tablet formulation (Figure 4a). The magnesium signal in the EDX spectrum was clearly seen in the core of the tablet and the samples taken at 2.5 minutes and 5 minutes (Figures 4a and 5). In the 15-minute sample the magnesium signal was clearly weaker than in the earlier samples. The 30-minute sample and later samples did not have a magnesium signal in the EDX spectrum (Figure 5). It would appear that after 15 minutes of coating, the polymer film covered the tablet surface almost completely and after 30 minutes the film covered the whole surface (Figures 4b and 5).

In batch 2 the magnesium signal was still visible after 2.5 and 5 minutes, but after 15 minutes of spraying the peak was not visible (Figure 5). The titanium peak was strong after 2.5 minutes of spraying and was at a similar level after 5 minutes (Figure 5). After 15 minutes the signal became stronger and at later time points the signal strength did not change remarkably (Figures 4c and 5).

Element mappings of magnesium and titanium (data not shown) were made by EDX analysis of the tablets. It

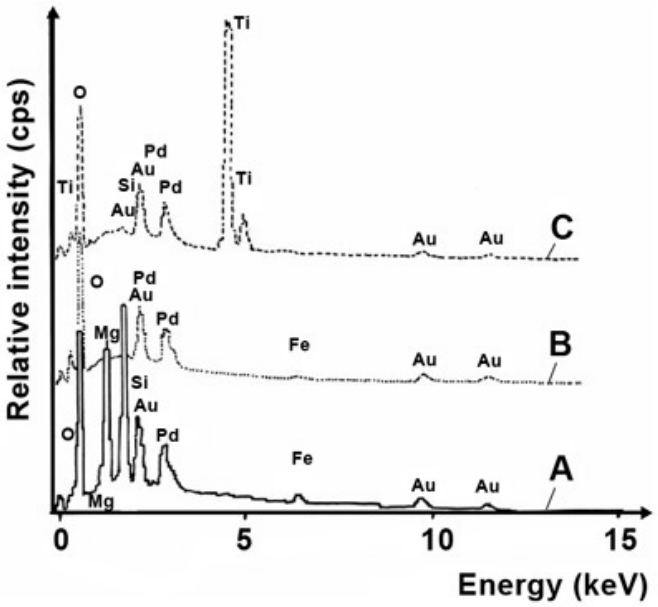

Figure 4. SEM-EDX spectra showing the inorganic elements in film-coated tablets during the coating process in a side-vented drum coater: (A) the core tablet, (B) the unpigmented film-coated tablet (batch 1), and (C) the pigmented film-coated tablet (batch 2).

seemed that magnesium (in batches 1 and 2) and titanium (in batch 2) were evenly distributed on the tablet surfaces at all time points.

Monitoring the Roughness

The core tablets were reasonably smooth, and the average roughness of the cores was 1.53 ± 0.16 µm. The roughness values cannot be compared with each other unless the resolution and the size of the measurement area are not

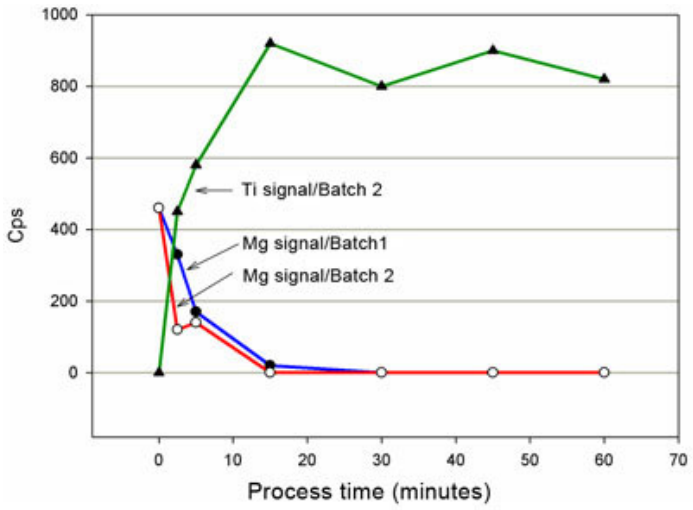

Figure 5. SEM-EDX results of the batch 1 and batch 2 tablets showing the development of magnesium and titanium signals during the coating process.

the same.[21] When the coating process began, the surface roughness also started to increase (Figure 6). Changes in roughness started to appear after 2.5 minutes of the process time, even though a very small amount of polymer solution had been applied (Figure 6). The increase of roughness at the beginning was most likely due to the dissolution effect of the polymer solution and mechanical wear caused by the mixing in the coater drum.[22] The increase in roughness was the greatest before the 15-minute point. Between 15 and 30 minutes the roughness increase was smaller, but the variation in the results was large. According to the SEM images and the EDX results, this was the same time period in which the coating covered the surface completely. Our findings were quite similar to those from earlier studies of Podczeck et al, who also monitored the film coating with laser profilometry and SEM.[11] Podczeck et al found that it took roughly 30 minutes to achieve a fully covering coating. The roughness of the tablets clearly increased, which is a quite commonly known feature of film coating.[23] In our study, the coated tablets from batch 1 and batch 2 did not have any statistically significant difference in roughness, which was also predicted since the amount of pigment was reasonably small.[23]

Comparison of the Techniques

Combining several analytical techniques such as SEM, EDX analysis, and laser profilometry gives a more well-rounded view of the development of film coating on tablet surfaces. Any one of these techniques cannot alone provide complete information about the surface. SEM gives a sharp image of the tablet surface, but it does not provide an exact numeric value for the surface roughness quantification. EDX extension of SEM can be used to locate elements both on the core and on the polymer coating, and it can be used to determine the process end point. Laser profilometry is a powerful noninvasive technique that gives quantitative 3D information from the tablet surface. With this technique, measurement of surface roughness is possible when the surface reflects more than 5% of the initial laser light. The reflection information from the profilometer can be used to follow the progress of the surface properties qualitatively. In the present study, we did not need any gold sputtering, since we were confident that laser light would reflect back sufficiently from the developing polymer film surface. However, Chopra et al used gold sputtering when measuring the surface roughness of polymer-coated pellets.[24]

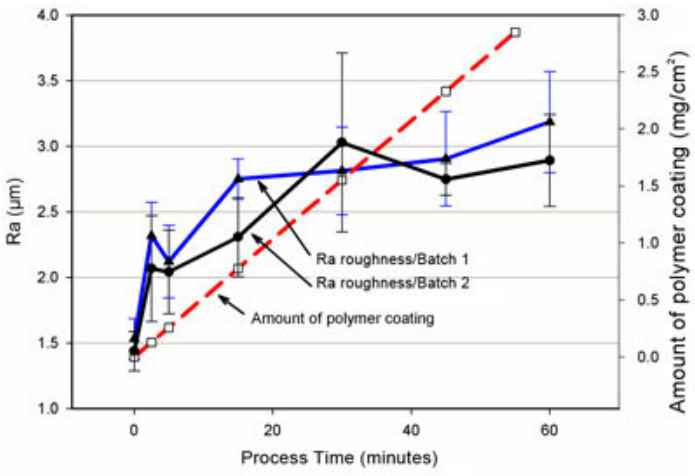

Figure 6. Laser profilometer roughness values and theoretical amount of polymer coating on the tablet surface as a function of process time in a side-vented drum coater for batch 1 unpigmented film coatings (n = 6) and batch 2 pigmented film coatings (n = 6). The broken line illustrates the theoretical amount of coating polymer applied (mg/cm^2) as a function of time. Ra indicates average roughness.

CONCLUSIONS

The laser profilometer results showed that the increase in surface roughness started from the beginning of the tablet coating process and that the largest increase in surface roughness occurred during the first 30 minutes of spraying. The SEM images and the EDX analysis results showed that the surface was fully covered within 15 to 30 minutes. It is necessary to combine the different measurement techniques to describe the polymer coating and to provide an insight into the development of surface roughness.

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