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Research paper

A novel technique for imaging film coating defects in the film-core interface and surface of coated tablets

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Abstract

Confocal laser scanning microscopy (CLSM) was introduced and examined as a novel technique for imaging film-core interface and surface defects of film-coated tablets. Tablets of acetylsalicylic acid, microcrystalline cellulose (MCC) and lactose monohydrate were film-coated with aqueous hydroxypropyl methylcellulose using an instrumented side-vented pan coater. The film coatings were applied using 100- and 500-kPa spraying air pressures. The CLSM images of the coating surface were compared with surface roughness measurements using a laser profilometer and an optical roughness analyzer. The spraying air pressure affected the film-core interface and the occurrence of coating defects. With the lower spraying pressure the aqueous coating solution penetrated into the tablet core, the core components migrated to the coating layer, and the film coating surface was clearly rougher compared to the higher spraying pressure. Storage at 25°C/60% RH or 40°C/75% RH for 3 months expanded the MCC-containing tablet core impaired the film structure and increased the film roughness. Based on the present results, CLSM is an effective tool for imaging film-core interface and surface defects of film-coated tablets. The CLSM images are supported by the results obtained with the other surface roughness measuring techniques.

Keywords: Confocal laser scanning microscopy; Film coating of tablets; Film-core interface; Film defects; Roughness

1. Introduction

In aqueous film coating, tablet cores may greatly interact with moisture during the spraying phase of the film coating process and subsequent storage. The water penetration into the tablet core could promote the expansion of the tablets and subsequently create internal stresses within the film coat and cause film coating defects [1,2]. During coating, the water penetration into the tablet core depends on a complex set of interacting factors related to the coating process and the formulation of the tablet and coating liquid [1–5]. For the formation of an adequate and adhesive film coat the atomized droplets have to spread completely over the surface of the tablet and limitedly penetrate into the tablet core. It is also possible that a drug or a core component migrates in or onto an applied film during coating or storage if the tablet has been exposed to high humidity [6–8].

The interactions between coating liquids and solids, such as droplet spearing, wetting and penetration tendencies, are usually measured with contact angle tests. These tests provide fundamental information (processing conditions aside), but do not reflect what may occur in practice when droplets of a coating formulation impinge on a surface during the coating process [4,9]. Therefore it would be important to clarify the behaviour of the coating liquid on the tablet surface and find the techniques required for acquiring exact information of the film-core interface. Confocal laser scanning microscopy (CLSM) has been used previously to investigate the deformation of particles during compression [10], the drug permeability and release mechanisms within controlled-release and enteric-coated pellets [11,12] and the diffusion of water-soluble drug from the pellet cores into the film layer [13]. CLSM is a non-invasive technique producing 3-D images of the surface or internal structure of the samples.

In the present study, CLSM was examined as a novel technique for imaging film-core interface and surface defects of film-coated tablets. The effects of spraying air

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pressure and short-term storage on aqueous hydroxypropyl methylcellulose (HPMC)-coated tablets were investigated. Laser profilometry and optical roughness analysis were used to provide numerical data on the surface roughness. The results of the surface roughness measurements and confocal images were compared.

2. Materials and methods

2.1. Tablet cores

The basic composition of the core tablets prepared for film coating was as follows: acetylsalicylic acid (Ph.Eur) 20.0%, lactose monohydrate (Pharmatose®, type 80M, DMV International, Veghel, the Netherlands) 35.5%, microcrystalline cellulose (Avicel®, type PH-102, FMC International, Cork, Ireland) 35.5%, talc (Ph.Eur) 8.0% and magnesium stearate (Ph.Eur) 1.0%. The basic direct-compression powder mixture (PM) was compressed with an eccentric tablet machine (Korsch EK0, Erweka Apparatebau, Germany) to a constant breaking strength of 60 N using 11-mm biconvex punches. The average weight of the tablets was 500 mg. After compression the tablets were stored for at least 1 week at controlled room conditions (22°C/50% RH).

To compare the expansion (i.e. water penetration) of microcrystalline cellulose (MCC) and the direct-compression PM in the tablet core, two types of tablet cores were prepared for surface profile examination (Fig. 1). The inner part of tablet A consisted of PM and the outer part of MCC. In tablet B, the order of the masses was the opposite. The inner compact was loosely compressed to a constant breaking strength of 20 N using 5-mm flat-faced punches. The inner compact was placed in the middle of the lower part of a 13-mm flat-faced punch and the tablet mold was manually filled with the outer mass. The tablet was compressed to a constant breaking strength of 60 N. After compression the tablets were stored for 4 days at two different relative humidity conditions of 22°C/50% RH and 22°C/95% RH to examine the water penetration to different parts of the tablet. The higher humidity condition was controlled using a saturated solution of potassium sulfate [14].

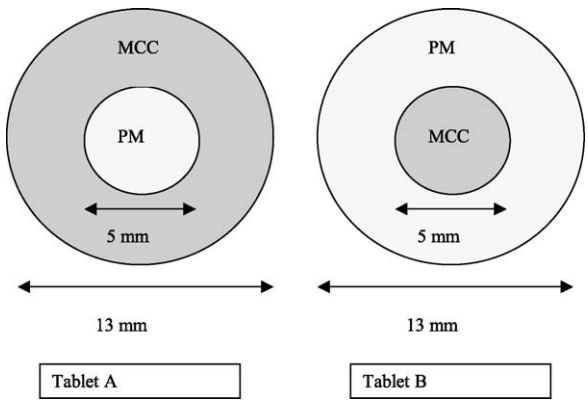

Fig. 1. Schematic diagram of the experimental tablet preparations used in surface profile examination. The inner part of tablet A consists of the basic direct-compression PM and the outer part of MCC. In tablet B, the order of the masses was the opposite.

2.2. Film coating of tablets

The coating solution was prepared of HPMC 8% w/w (Hypromelloc E5®, Dow Chemical, Midland, MI, USA), glycerol (Fluka Chemic AG, Buchs, Switzerland) 20% w/w of polymer weight, riboflavin sodium phosphate (Ph.Eur) 0.5% of solution weight and purified water (Ph.Eur). An autofluorescent agent, riboflavin sodium phosphate, was included in the coating solution (i.e. fluorescent coating) to provide good contrast against the core material when studied with confocal laser scanning microscopy. The amount of coating solution applied was 300 g. The basic direct-compression PM tablets were film-coated using a pilot-scale, side-vented, instrumented and automated pan-coating apparatus (Thai coater, model 15, Pharmaceuticals and Medical Supply Ltd. Partnership, Thailand) [15]. Two different spraying air pressures, 100 and 500 kPa, were applied. The other user-controllable process parameters were adjusted to the following values: pan air temperature 40°C, coating solution flow rate 5.7 g/min, outlet airflow rate 18 l/s, inlet air absolute humidity 12 g/m^3, pan air pressure −5 Pa and rotating speed of pan 7 rpm. Each coating batch comprised 1.0 kg of tablets. Before spraying, the tablets were preheated for 5 min, and dried for 5 min after spraying. After the film coating the tablets were stored in closed glass bottles at controlled conditions of 25°C/60% RH or 40°C/75% RH for 3 months.

2.3. Confocal laser scanning microscopy

The film-coated tablets were examined using CLSM. Observations were made with a Bio-Rad Lasersharp MRC-1024 (Bio-Rad, UK) attached to a microscope (Axiovert 135M, ZEISS, Germany) using a Zeiss Plan-Neofluar 10x/0.30 NA air lens. A 488-nm line of a krypton-argon laser and a laser power of 0.15 mW were used. The iris, black, gain control and all other settings were kept constant during all experiments. Kalman for $N = 6$ frames per Z level was set prior to initiation of the Z series. Images were recorded at intervals of 5 μm in the Z direction. The confocal aperture setting was 1.1 mm. The figures were maximum projection.

The images were measured by comparing the fluorescence intensity of riboflavin sodium phosphate in the coating with that of the core tablet (non-fluorescent area). Each stack of pictures was evaluated using an image analysis system (ImageSpace, Molecular Dynamics, Inc., USA). The confocal image area was 7578 × 7578 μm. The 3-D plots were calculated based on quantified riboflavin intensity values and represent the same surface areas as the corresponding confocal images. The randomly sampled

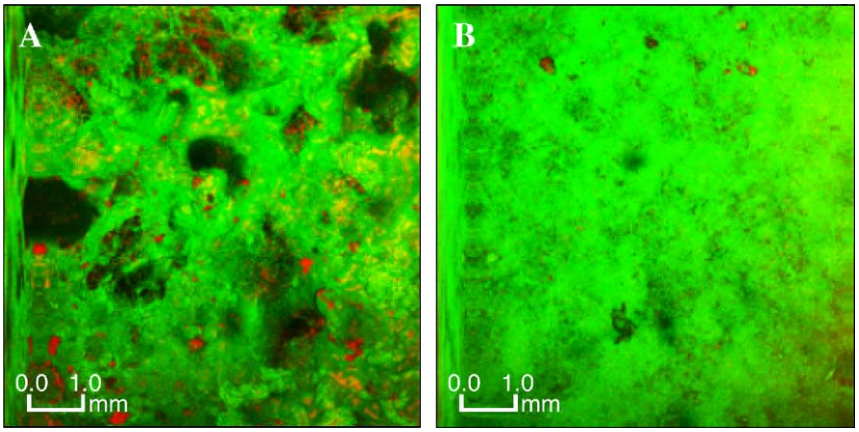

Fig. 2. Confocal images of the HPMC film coating immediately after coating. The coatings were applied with spraying air pressures of 100 kPa (A); and 500 kPa (B). The coating appears green and red indicates components migrated from the tablet core.

tablets were imaged immediately after the film coating and after 3 months' storage in both controlled conditions.

2.4. Laser profilometry

The tablets surface roughness was measured using a non-contacting laser profilometer (UBM Microfocus Measurement System, UBM Mebtechnik GMbH, Ettlingen, Germany). Details of the method have been published elsewhere [16,17]. An area of 3 × 3 mm was scanned from the upper surface of three randomly sampled tablets. The roughness parameters were calculated from data measured with 125 pixels/mm x-y resolution and 0.1 μm of z resolution. The measurement frequency was 120 pixels/s. The roughness parameter measured was the arithmetic average of the absolute values of all points of the profile (Ra) and the maximum distance between the highest point and the mean line of the profile (Rp). The roughness was measured from core tablets and coated tablets immediately after film coating and after 3 months' storage in the two controlled conditions.

The surface profiles of the two tablet core types (MCC and PM) were measured by scanning an area of 8 × 8 mm. The roughness parameters were calculated from data measured with 50 pixels/mm x-y resolution and 0.1 μm of z resolution. The measurement frequency was 120 pixels/s. The image data was transferred to Mathematica software (Wolfram Research Inc., USA) that was used to draw 2-D surface plots to compare the expansion of MCC and PM in the tablet core.

2.5. Optical roughness analysis

The coated tablets surface roughness was measured also using an optical technique, introduced in Krogars et al. [18]. The imaging unit including a light source and a CCD camera (JAI, CV-M50, Copenhagen, Denmark) with a lens objective was connected to a frame grabber (WinTV, Hauppauge Computer Works Inc., Hauppauge, NY, USA) and a PC. The illumination system included a lamp housing (Model 60000, Series Q Housing, Oriel Instruments, Stratford, CT, USA), a 100-W quartz Tungsten halogen lamp and a collimating lens assembly (Oriel Instruments, Stratford, CT, USA). The light source was connected to a stabilized DC power supply (model 68735, Oriel Instruments, CT, USA).

The following setup was used: light source power supply voltage 5 V, distance of the light sources to the sample 10 cm, illumination angle 58° and dimmer set to 8. A 50-mm lens objective with a 40-mm extension tube was used (focal length 1.3). The images of tablets were taken in a dark room. Ten images of 6.2 × 4.7 mm surface area of each tablet were taken with a resolution of 600 × 800 pixels. Three randomly sampled tablets were imaged immediately after the film coating and after 3 months' storage in the two controlled

Table 1
Effects of spraying air pressure and storage conditions on tablet roughness parameters measured using a laser profilometer[a]

	Tablet core		Coated tablet			
	Ra	Rp	Ra[b]	Rp[b]	Ra[c]	Rp[c]
0 months –	0.9 (14.5)	5.2 (17.5)	11.5 (2.5)	114.8 (15.8)	4.2 (16.5)	26.9 (37.2)
3 months 25°C/60% RH	2.4 (11.9)	16.4 (37.1)	12.0 (32.4)	98.2 (37.5)	6.2 (42.2)	22.2 (28.7)
3 months 40°C/75% RH	8.3 (28.3)	60.9 (55.5)	19.8 (31.9)	119.7 (26.3)	10.8 (13.8)	78.0 (3.2)

[a] Mean μm (R.S.D. %), $n = 3$.
[b] Spraying pressure 100 kPa.
[c] Spraying pressure 500 kPa.

Table 2
Effects of spraying air pressure and storage conditions on tablet roughness parameters measured using an optical roughness analyzer[a]

Storage time	Storage conditions	Spraying air pressure	
0 months	–	7.2 (10.6)[b]	3.0 (22.8)[c]
3 months	25°C/60%RH	8.2 (18.4)[b]	3.7 (13.7)[c]
3 months	40°C/75%RH	8.5 (25.8)[b]	4.2 (19.2)[c]

[a] Mean (R.S.D. %), $n = 3$.
[b] Spraying air pressure 100 kPa.
[c] Spraying air pressure 500 kPa.

conditions. The roughness was measured from a matrix formed by the numerical gray scale values of the image using Mathcad 2001 Professional software (MathSoft Inc., USA). Seven parallel profile lines were extracted from the matrix with 75 rows between each line. The lines consisted of the gray scale values of the 800 horizontal pixels. Roughness is the arithmetic average of the absolute values of all points (pixels) of the profile.

2.6. Scanning electron microscopy

The morphology and crystal growth in the tablet film coat was studied by scanning electron microscopy (SEM) by taking micrographs (Zeiss DSM-962, Carl Zeiss, Germany).

3. Results and discussion

3.1. Effect of spraying air pressure on film-core interface and film surface

The effects of the spraying air pressure on the film surface are illustrated in CLSM images (Fig. 2). With the lower spraying air pressure (100 kPa), clear film defects and roughness were observed on the coating surface compared to the higher spraying air pressure applied (Fig. 2, Tables 1 and 2). CLSM images show relatively large gaps (i.e. non-fluorescent areas) in the coating surface (Fig. 2A). Some component(s) from the core, probably the water-soluble lactose, migrated into the coating during the coating process (Fig. 2A). With the lower spraying air pressure, larger droplets were formed allowing water to penetrate into the tablet core and increased the migration of the component to the coating. Consequently, the spreading and drying of the coating solution were prolonged, which increased the surface roughness. It has been reported earlier that coating conditions can affect water penetration to the substrate (i.e. the rate of water evaporation) during the coating process and subsequently the migration of water-soluble components of the tablet core to the film coating [7,8]. If components of the core migrate into the film layer

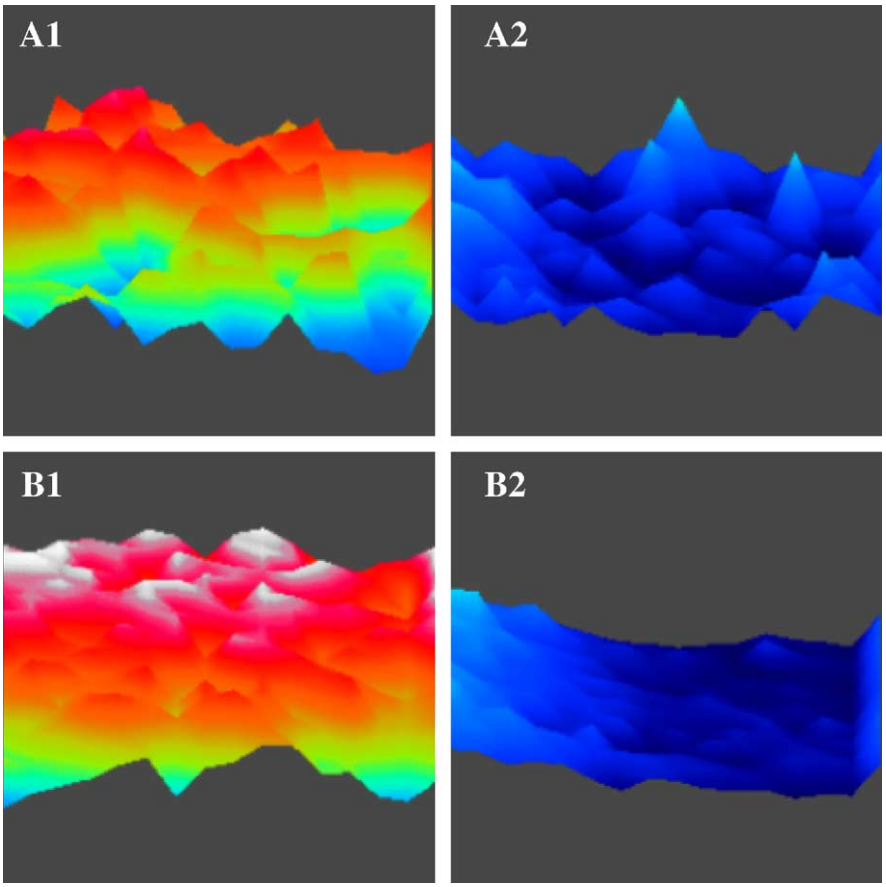

Fig. 3. 3-D plots of the HPMC film coating (1); and tablet core (2) immediately after coating. The coatings were applied with spraying air pressures of 100 kPa (A); and 500 kPa (B). Red colour indicates the topmost coating layer, green the coating layer near the tablet core and blue the non-fluorescent tablet core.

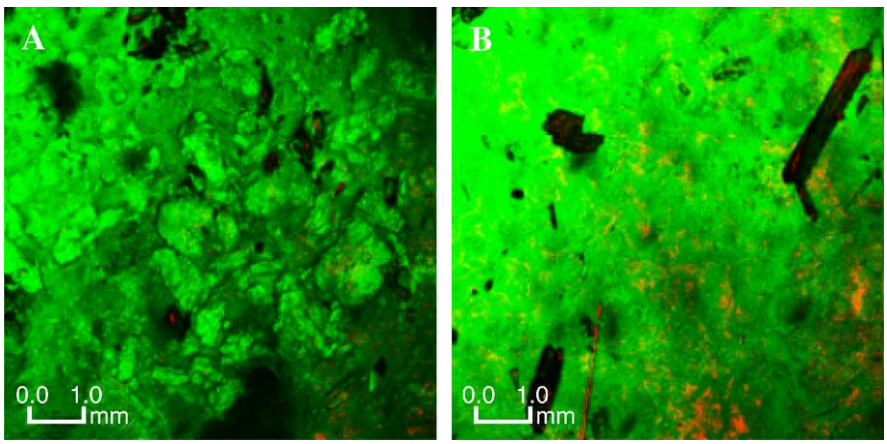

Fig. 4. Confocal images of the HPMC film coating immediately after coating after storage of 3 months at 40°C/75% RH. The coatings were applied with spraying air pressures of 100 kPa (A); and 500 kPa (B). The coating appears green and red indicates components migrated from the tablet core.

during the early stages of the coating process, it could lead to unhomogeneous film formation [7].

The 3-D plots (Fig. 3) illustrate the film-core interface and represent the same surface areas as the corresponding confocal images (Fig. 2). With the lower spraying air pressure (100 kPa) the applied film coating solution was unevenly distributed and the thickness varied in different parts of the film (Figs. 3A1). The aqueous coating solution penetrated significantly into the inner regions of the tablet core and formed 'valleys' on the core surface (Fig. 3A2). Variation in film thickness, due to coating solution penetration and surface roughness, may be important

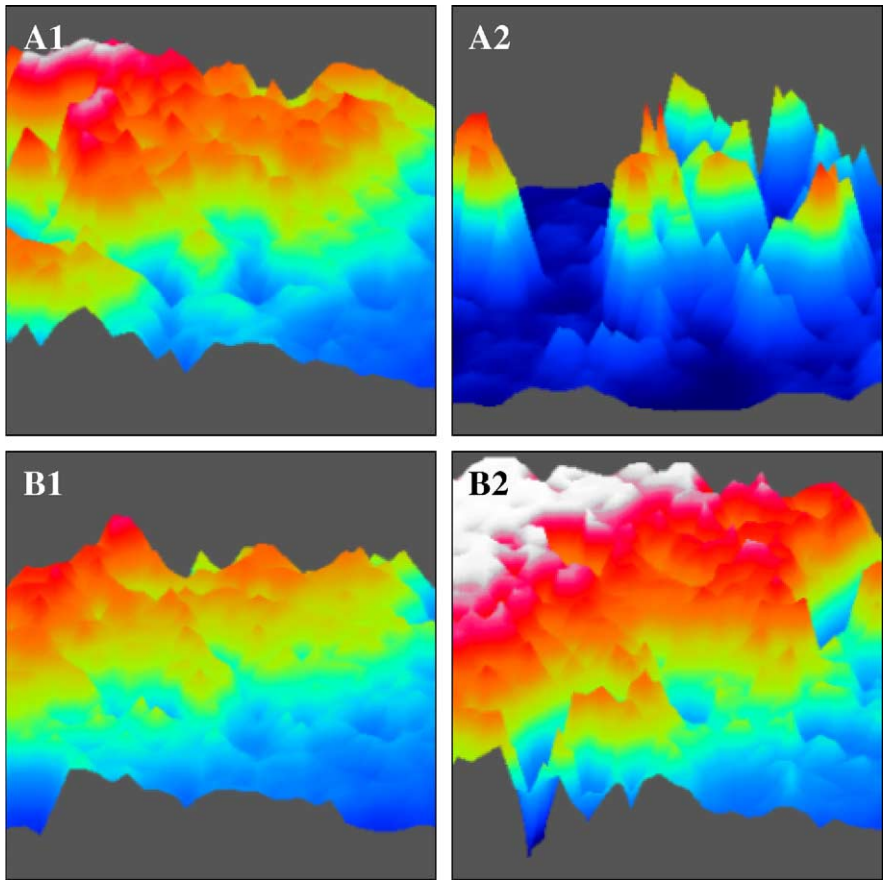

Fig. 5. 3-D plots of the HPMC film coating after storage of 3 months at 25°C/60% RH (1); and at 40°C/75% RH (2). The coatings were applied with spraying air pressures of 100 kPa (A); and 500 kPa (B). Red colour indicates the topmost coating layer, green the coating layer near the tablet core and blue the non-fluorescent tablet core.

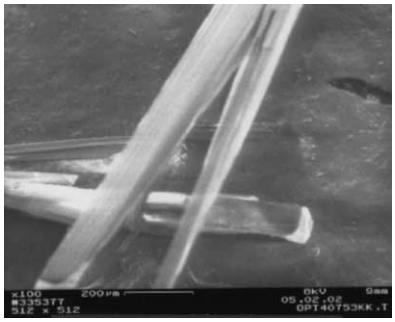

Fig. 6. Scanning electron micrograph of the film-coated tablet surface after a storage period of 3 months at 40°C/75% RH. The coatings were applied with a spraying air pressure of 500 kPa.

when the properties of the film coat are dependent on the thinnest part of the coating, especially in case of modified drug release coatings [4,7,19–23].

With the higher spraying air pressure (500 kPa) the coating surface was uniform and smooth compared to the lower spraying air pressure applied (Fig. 2B, Tables 1 and 2). The migration of core components into the coating was minimal (Fig. 2B). The film coating solution was homogeneously distributed onto the tablet core (Fig. 3B1). The solution did not penetrate perceivably into the core, and the surface of the core was even (Fig. 3B2). With the higher spraying air pressure, fine droplets were formed, thus improving the spreading and water evaporation of the film, which reduced the degree of solution penetration into the tablet core and produced smoother and denser films. These results are in agreement with Twitchell et al. [4,23] who reported that with increasing atomizing air pressure the surface roughness of the coated tablets decreases.

3.2. Effect of storage on film surface

The effects of storage at 40°C/75% RH for 3 months on the film surface are illustrated in CLSM images (Fig. 4). The surface roughness and film defects increased (Fig. 4, Tables 1 and 2) compared to the initial situation (Fig. 2, Tables 1 and 2). The film structure illustrated by the 3-D plots in Figs. 5A2,B2 represents the same surface areas as the confocal images in Fig. 4 (A and B, respectively). The internal structure of the film coatings deteriorated when the tablets were stored at 25°C/60% RH (Figs. 5A1,B1) and 40°C/75% RH (Figs. 5A2,B2) for 3 months. Coating sprayed with 500-kPa air pressure remained clearly better and more homogeneous (Fig. 5B2) than coating sprayed

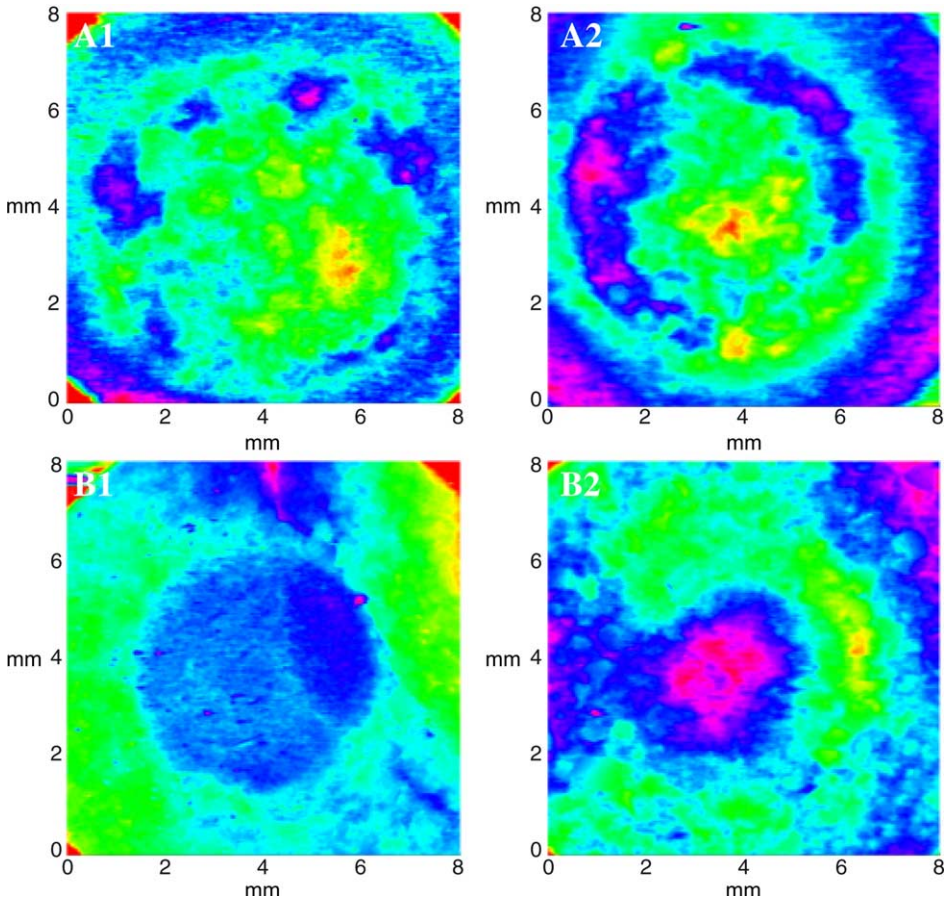

Fig. 7. Surface profiles of tablet A with a basic direct-compression PM in the centre and of tablet B with MCC in the centre. The tablets were stored for 4 days at 22°C/50% RH (1); and 22°C/95% RH (2). Reference is made also to Fig. 1. Colours from the highest to lowest elevation: aniline red, blue, green, yellow, bright red.

with the lower air pressure (Fig. 5A2). With 500 kPa the surface also remained smoother (Fig. 4, Tables 1 and 2).

As seen in the CLSM images (Fig. 4) and the SEM micrograph (Fig. 6), needle-like crystals appeared around the film coatings of tablets within 3 months of storage at 40°C/75% RH. It has been reported earlier that the migration of salicylic acid into the applied film coating can occur because of its sublimation tendency during storage at elevated humidity [24]. The present stress storage conditions accelerated hydrolysis of acetylsalicylic acid to salicylic acid and acetic acid.

The surface profile measurements of the two types of tablets showed that the presence of microcrystalline cellulose (MCC) in the outer (Figs. 7A1,A2) or inner part of the tablets (Figs. 7B1,B2) led to greater tablet surface profile expansion of these regions compared to direct-compression PM. MCC expanded (i.e. water penetrated) clearly already in 50% RH (Figs. 7A1,B1) and expansion further increased in elevated humidity (95% RH) (Figs. 7A2,B2). In addition, the surface roughness of core tablets clearly increased during storage, indicating that the cores absorbed water (Table 1). These results are in agreement with earlier studies in which MCC absorbed water rapidly and expanded due to pore widening [3,5,25]. In this study, impaired film structure and increased surface roughness of film-coated tablets were mainly caused by expansion of the tablet core due to MCC hydration during storage. This core expansion resulted in increased internal stresses in the films and subsequent deterioration of the film structure. Adverse changes in the film structure during storage at high humidity have been reported previously to result from adsorbed water acting as a plasticizer, which induced swelling, increased polymer chain mobility, deformation and flexibility [24,26].

3.3. Comparison of CLSM and other surface roughness measuring techniques

The CLSM technique shows clear differences in the film-core interface and surface structure between coatings applied with different spraying air pressures. CLSM is a suitable method for studying the film-core interface and surface defects, as it only visualizes fluorescent materials (in this case coating). Non-fluorescent materials (in this case the tablet core) are not detected. The results obtained by CLSM and the other two surface roughness measuring techniques, laser profilometry and optical roughness analysis, were comparable (Figs. 2–5, Tables 1 and 2). The measurement accuracy and speed of the last two methods are not, however, completely comparable as the laser profilometer was set to measure approximately 20 times more data than the optical roughness analyzer, but with this setup the optical roughness analysis was a quick method. By either method nearly the whole surface of the tablet can be evaluated. In an earlier study the roughness values obtained by laser profilometry were found to correlate with those found with the optical roughness analysis technique [18]. The images produced by the CLSM method supported the findings of the numerical roughness measurements.

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