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Development of an Automation System for a Tablet Coater

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ABSTRACT An instrumentation and automation system for a side-vented pan coater with a novel air-flow rate measurement system for monitoring the film-coating process of tablets was designed and tested. The instrumented coating system was tested and validated by film-coating over 20 pilot-scale batches of tablets with aqueous-based hydroxypropyl methylcellulose (HPMC). Thirteen different process parameters were continuously measured and monitored, and the most significant ones were logged for analysis. Laser profilometry was used to measure the surface roughness of the coated tablets. The instrumentation system provided comprehensive and quantitative information on the process parameters monitored. The measured process parameters and the responses of the film-coated tablet batches showed that the coating process is reproducible. The inlet air-flow rate influenced the coating process and the subsequent quality of the coated tablets. Increasing the inlet flow rate accelerated the drying of the tablet surface. At high inlet flow rate, obvious film-coating defects (ie, unacceptable surface roughness of the coated tablets) were observed and the loss of coating material increased. The instrumented and automated pan-coating system described, including historical data storage capability and a novel air-flow measurement system, is a useful tool for controlling and characterizing the tablet film-coating process. Monitoring of critical process parameters increases the overall coating process efficiency and predictability.

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INTRODUCTION

In the pharmaceutical industry, aqueous-based film coating of tablets is usually performed using different kinds of side-vented (perforated) pan coaters. Film coating of tablets is a complex and multivariate process and, consequently, a rather sensitive manufacturing step. The problem is how to control the pharmaceutical quality of the final products and the variance between batches. The effects of process conditions of a side-vented pan coater are not very well characterized or understood, probably because of the lack of effective instrumentation systems. Only a few previous reports have been published on the topic [1,2].

One of the most important tasks during film coating is to control and measure the critical process parameters [1,3]. If the process conditions during the film coating were better characterized, more satisfactory coating results could be achieved. An automated film-coating system capable of monitoring the process is a useful tool for controlling the process and understanding the related phenomena.

In the present study, an automated pilot-scale side-vented pan coater with an air flow rate measurement system was designed, calibrated, and tested. The instrumentation concept (including process control displays) was kept simple, focusing on the improvement of system operation and real-time monitoring of the film-coating process. Special attention

was paid to using the instrumentation to measure and control the properties of the coated tablet.

MATERIALS AND METHODS

Instrumentation and automation of the pan coater

The instrumentation was carried out and the tablets were film-coated using a pilot-scale side-vented pan-coating apparatus (Thai Coater, Model 15, Pharmaceuticals and Medical Supply Ltd Partnership, Bangkok, Thailand) (Figure 1). The instrumentation covered 13 different coating-process parameters, which were measured and monitored continuously (Table 1 - symbols refer to Figure 1). The process parameter operation ranges are listed in Table 1.

The developed automated system uses system architecture similar to the one described by Rantanen et al [4] but with different instrumentation and device (side-vented pan coater). In the present setup, the InTouch 7.0 version of FactorySuite 2000 (Wonderware Corp, Irvine, CA) was used as the user interface in which the process control display and examples of typical historical and real-time film-coating trendlines were presented (Figure 2 - symbols refer to Figure 1 and Table 1). The process parameters were adjusted within their operation ranges from the user interface. Windows NT 4.0 (Microsoft Corp, Redmond, WA) was used as the operating system in a Pentium PC.

The rotating speed of the motor and thereby the rotating speed of the pan as well as the air flow rate were controlled using a frequency transformer (Movitrac 31C, SEW Eurodrive, Bruchsal, Germany). The pressurized air unit consisted of an Electro/Pneumatic (E/P) converter (range 0.005-0.5 MPa, ITV-2030, SMC Pneumatics, Tokyo, Japan), and the pressurized air was filtered (TAIYO EAF-10 / ERF-10, SMC Pneumatics). The spraying air pressure was checked with a pressure-measuring instrument (VDO-IMT 1875, Tecalemit, Helsinki, Finland). The absolute humidity of the inlet air was adjusted with an air humidity controller (Ilmasäätö Oy, Turku, Finland). The inlet air temperature was controlled using a heat controller (TTC 25 Regin, AB Regin, Kållered, Sweden). The spraying was performed with a pneumatic nozzle (Air Atomizing 1/4 JAU-SS, Spraying Systems Co, Wheaton, Illinois, USA). The coating liquid was pumped using a peristaltic pump (Watson-Marlow 504Du pump, Smith & Nephew Watson-Marlow, Falmouth, UK).

Instrumentation and calibration of the process air-flow rate system

Process air-flow measurement was performed using separate flow tubes (Ilmasäätö Oy, Turku, Finland). The monitored inlet and outlet air-flow rate was based on the pressure difference between the flow tubes. The size and structure of the tubes were optimized off-line in addition to calibrating the pressure transmitters (Produal PEL-N, Produal PD, Karhula, Finland). The air-flow measurement was calibrated off-line. The pressure transmitters output from the flow tubes was calibrated against a valid reference. The voltage output of the pressure transmitters was measured 5 times. The calibrated ranges and results of the measurements are presented in Table 2.

Temperature was measured using Pt-100 type sensors (Mikor, Turku, Finland) with a fast response time. All temperature sensors were calibrated in a water bath. For each temperature, 10 measurements were made after 3 minutes of equilibration (Table 2).

The relative humidities of the process air were measured using capacitive humidity sensors (Humicap, Vaisala Oyj, Vantaa, Finland) and humidity and temperature transmitters (Humicap 233, Vaisala Oyj). Absolute humidity was calculated from the relative humidity and temperature. The relative humidity and temperature sensors were checked with a humidity calibrator (HMK15, Vaisala Oyj). Humidity sensors were calibrated at room temperature (22°C) using saturated electrolyte solutions (LiCl, NaI, NaCl) with different relative humidities. Five measurements were made after 10 minutes of equilibration (Table 2).

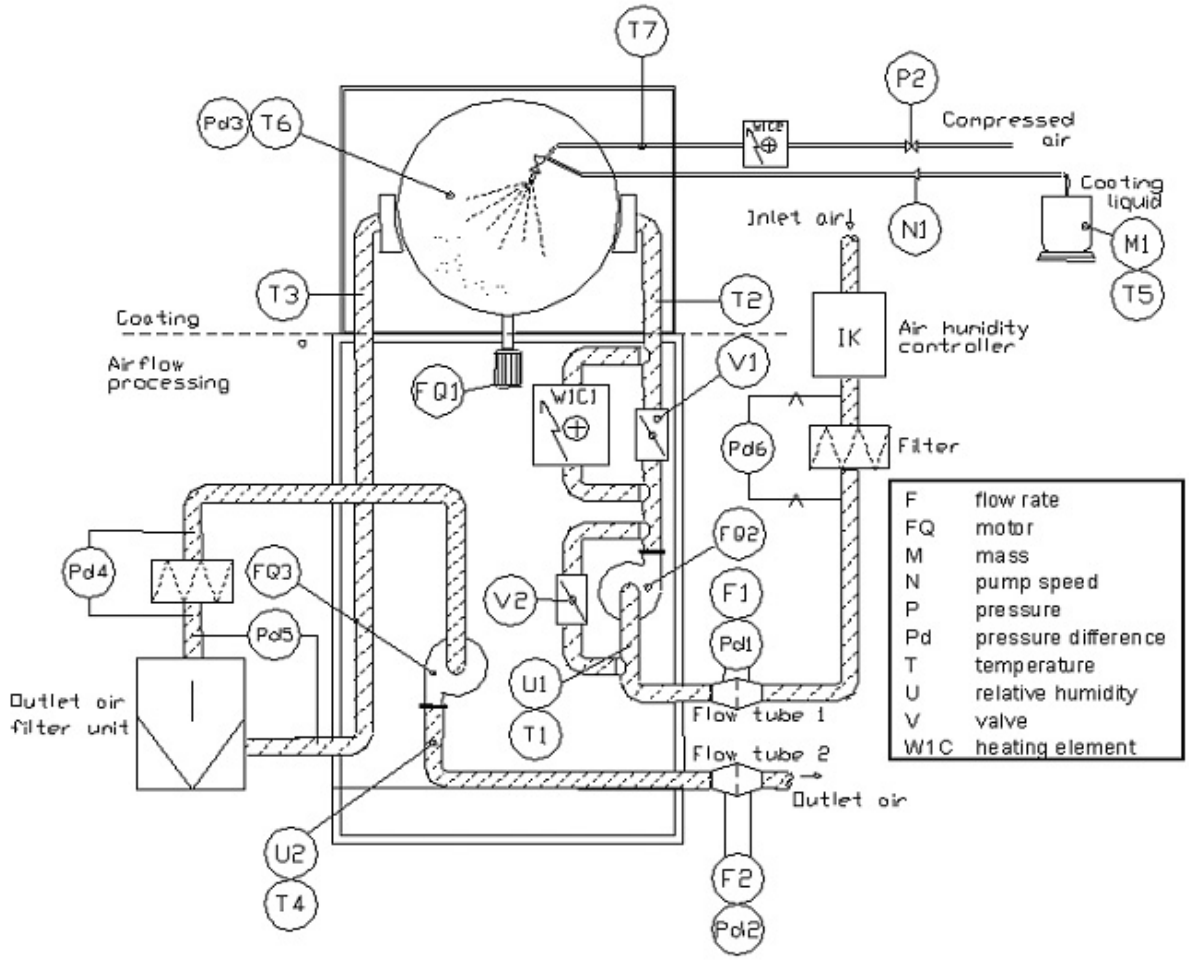

Figure 1. Instrumentation of the pan coater.

Process data

The process information during coating was logged for further analysis. The Historical Data Management (Wonderware Corp, Irvine, CA) application was used to access the historical data files created by InTouch (part of FactorySuite 2000, Wonderware Corp) and to convert the data files to a format compatible with MS Excel, for example. In this study, process data consisted of the critical process parameters at 5-second intervals: inlet air temperature (T1, T2), inlet air relative humidity (U1), inlet air flow rate (F1), outlet air temperature (F4), outlet air relative humidity (U2), outlet air-flow rate (F2), pan air temperature (T6), and negative pan air pressure (Pd3).

Materials used in the film coating

Initial coating trials were performed using the basic HPMC coating liquid prepared of Opadry OY-GM-22902 (Colorcon, Dartford, UK) dry powder and purified water (Ph. Eur.). In the film-coating process, 10% wt/wt solid liquids were used. The amount of coating liquid was 300 g. Each coated batch comprised 1.0 kg of tablets. Before the spraying procedure, the tablets were preheated in a pan

Table 1. Summary of Monitored Process Parameters

Process parameter	Symbol	Operation range
Inlet air flow rate	F1	0…25 L/s
Inlet air temperature	T1, T2	0…100ºC
Inlet air relative humidity	U1	0…100%
Inlet air absolute humidity	AH1	0...12 g/m^3
Outlet air flow rate	F2	0…25 L/s
Outlet air temperature	T3, T4	0…100ºC
Outlet air relative humidity	U2	0…100%
Outlet air absolute humidity	AH2	0...100 g/m^3
Pan air temperature	T6	0…100ºC
Negative air pressure (pan)	Pd3	-50…+50 Pa
Rotating speed of the pan	FQ1	3…30 rpm
Temperature (coating liquid)	T5	0…100ºC
Pump speed (flow rate)	N1	0…55 rpm
Spraying air pressure	P2	0…500 kPa
Spraying air temperature	T8	0…100ºC
Coating liquid mass	M1	0…24 000 g

coater for 10 minutes and, following the spraying, the tablets were dried in a pan coater for 5 minutes and then at room temperature (22 ± 1°C) for at least 24 hours.

The composition of the core tablets used in the experiments was as follows: ibuprofen (Ph. Eur.) 30%, lactose monohydrate (Lactose NF Tablettose, Meggle, Wasserburg, Germany) 23%, microcrystalline cellulose (MCC, Emcocel 90M, Edward Mendell Co, Nastola, Finland) 46%, and magnesium stearate (Ph. Eur.) 1%. The tablets were produced in a rotating tablet machine (Kilian & Co, GmbH, Köln, Germany) to a constant breaking strength of 95-100 N using 11-mm biconvex punches.

Testing of the reproducibility of the coating process

To test the instrumentation system and the reproducibility of the coating process, over 20 coating experiments were conducted. To evaluate the reproducibility of the process, 4 experiments were performed under identical conditions. The levels of the user-controllable coating parameters were adjusted to the following values:

Outlet air flow rate (F2)	20 L/s
Pan air temperature (T6)	40°C
Negative air pressure (pan) (Pd3)	5.0 Pa
Rotating speed of the pan (FQ1)	7.0 rpm
Temperature (coating liquid) (T5)	20°C
Pump speed (flow rate) (N1)	2.8 rpm
Spraying air pressure (P2)	300 kPa

Testing of the process air flow rate system

To test the effects of the process air flow rate on the coating process and on the properties of the coated tablets, the outlet air flow rates (F2) were adjusted to 12 L/s (minimum), 18 L/s, and 24 L/s (maximum). In these experiments, the other user-controllable coating parameters were as mentioned above, and the experiments were repeated twice.

The loss of coating material was measured so that the filter was placed on top of the outlet air flow rate tube, and the filter was weighted before and after the coating experiment. The loss of coating material was also determined by measuring the mass balance of the coating process.

Evaluation of the film-coated tablets

The responses evaluated were physical appearance (film quality) (visual and microscopy image analyzer, Leica MZ 6, Solms, Germany), surface roughness (noncontacting laser profilometer, UBM Microfocus Measurement System, UBM Messtechnik GMbH, Ettlingen, Germany), weight (n = 20), height (Sony Micrometer, Sony Magnescale Inc, Tokyo, Japan), and breaking strength (Erweka Multicheck, GWB, Hausenstamm, Germany) of the film-coated tablets.

The roughness parameter measured was the arithmetic average of the absolute values of all points of the profile (Ra). Details of the profilometry have been published elsewhere [5,6,7]. The upper surface in the centre of the 10 tablets was measured by scanning an area of 3 x3 mm. The roughness parameters were calculated from data of 125 pixels/mm x-y resolution and 0.5 mm of z resolution. The measured frequency was 120 pixels/s.

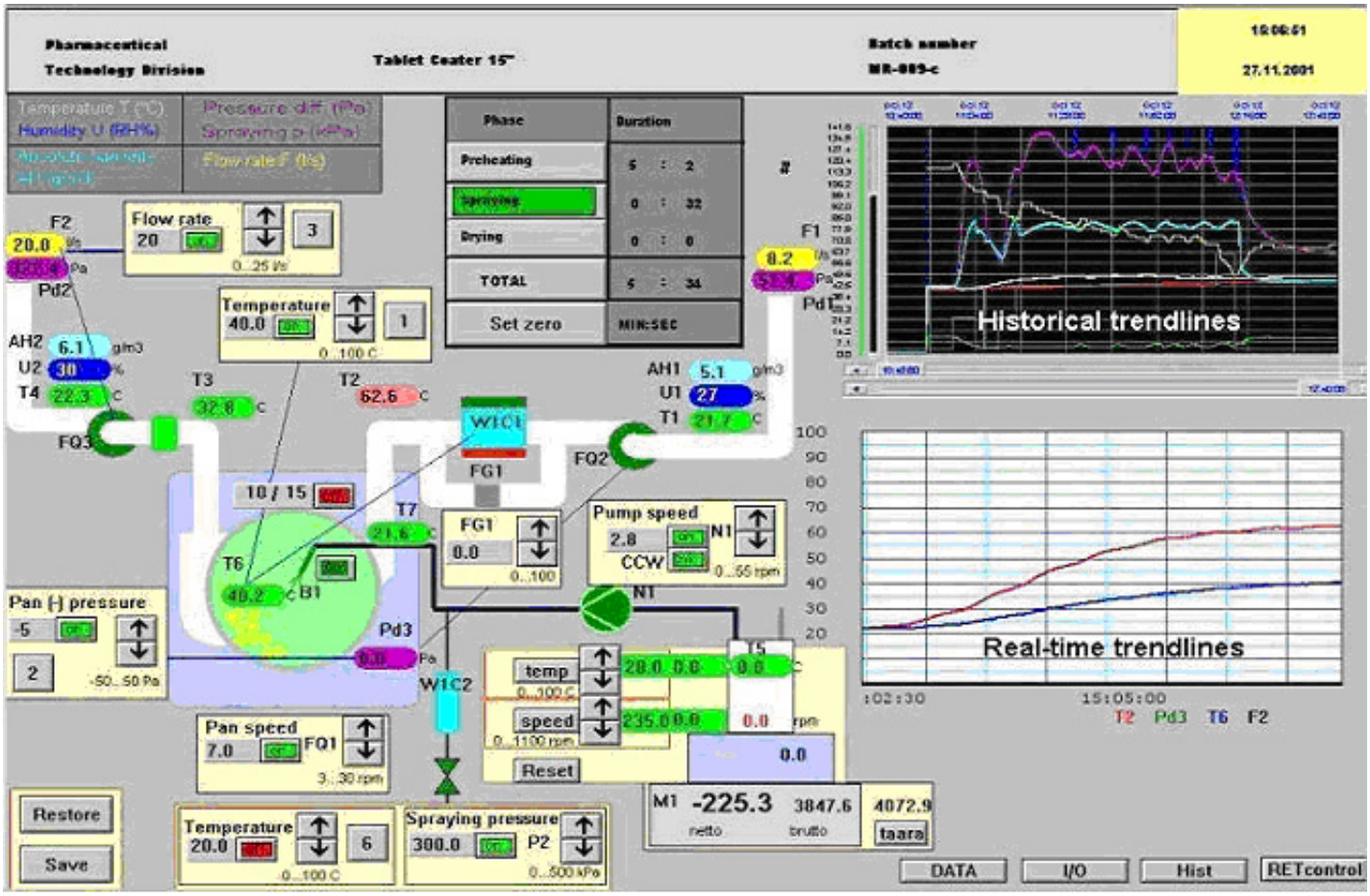

Figure 2. User interface of the instrumented pan coater.

RESULTS AND DISCUSSION

Measuring and controlling the reproducibility of the coating process

Process information of the 4 repeated coating experiments with identically set process values is shown in Figures 3-6. The trendlines show the behavior of critical process parameters during the preheating, spraying, and postdrying phases. The trendlines of key process parameters provide comprehensive documentation of each coating experiment.

Figure 3 shows the behavior of the process inlet air flow rate (F1), outlet air flow rate (F2), and negative pan air pressure (Pd3) during different phases of the coating process. The preheating phase F1, F2, and Pd3 reached the adjusted values. The F1 (12 L/s) was lower than the user-controllable F2 (20 L/s), as expected. The user-controllable Pd3 remained at the set value (-5 Pa) and was used to control F1. When the spraying phase started, the Pd3 increased for a few seconds. The process information proved that the air flow rate measurement system operated reliably.

Figure 4 demonstrates a typical behavior of process inlet air temperature and pan air temperature during different coating process phases. During the preheating phase, the user-controllable pan air temperature (T6) reached the set value (40°C). The initiation of the spray phase caused a slight and brief drop and variation in T6 due to water evapora-

Table 2. Process Air Calibration Results

Measurement	Results		
Reference value of air flow rate (L/s)	10.0	15.0	20.0
Inlet air flow rate (L/s)	10.0±0.9	15.0±1.1	20.0±0.6
Outlet air flow rate (L/s)	10.0±1.0	15.0±0.8	20.0±0.6
Reference value of temperature °C	0.1	50.0	99.9
Inlet air temperature (T2) °C	0.2±0.1	50.3±0.0	99.9±0.2
Outlet air temperature (T3) °C	0.1±0.1	50.2±0.0	99.8±0.2
Pan air temperature (T6) °C	0.2±0.1	50.2±0.0	99.9±0.2
Reference value of temperature °C	22.0		
Inlet air temperature (T1) °C	22.0±0.2		
Outlet air temperature (T4) °C	22.0±0.2		
Reference value of relative humidity RH%	11.4	40.0	75.5
Inlet air relative humidity (U1) RH%	12.2±0.4	39.2±0.4	75.0±0.0
Outlet air relative humidity (U4) RH%	12.2±0.4	42.6±0.5	75.0±0.0

tion. A decrease of water evaporation in the post-drying phase caused a slight rise in T6, and the inlet air temperature (T2) decreased rapidly. It can be seen that as T6 begins to increase above the set value, it causes a corresponding decrease in T2, and vice versa. The lag time between changes in T2 and T6 is minimal, as can be seen in the sinoidal shape curves. The sinoidal shape in the temperature data is caused by the PID (Proportional-Integral-Derivative) control loop. The inlet air temperature (T1) (before the heater) was 23 ± 1°C in all experiments. Measuring the pan air temperature helps to control the film-coating process and, consequently, enables the prevention of possible premature drying or overwetting problems, which may result in poor appearance and film quality [8].

Figures 5 shows the behavior of inlet air absolute humidity (AH1) and outlet air absolute humidity (AH2) during different phases of the coating process. The AH2 was stable in the preheating phase and increased rapidly at the initiation of the spray phase due to evaporation of water. In the postdrying phase, AH2 decreased rapidly. In the preheating phase, it was higher than AH1 due to heat-induced water evaporation from core tablets. The level of humidity from experiment to experiment was not as constant as other process parameters (Figures 3, 4). Changes in ambient room air humidity obviously affected the levels of inlet air humidity of the coating process to some degree. The air humidity controller (IK) (Figure 1) is under further development to better adjust and maintain the set inlet air humidity.

According to the literature, during the spraying phase before the spray reaches the tablet bed, water evaporation causes decrease in the pan air temperature [3,8,9]. The inlet air humidity changes have been seldom measured in previous coating application studies [3,8]. In this study, AH2 of the process air (Figure 5) was a more reliable indicator of water evaporation during the coating process than pan air temperature (Figure 4; T6). The changes in inlet air humidity not only alter the temperature of the spray but also influence the amount of water evaporated before the spray reaches the tablet bed.

The convergence of the absolute humidity of the outlet and inlet air at the end of the drying phase is used as an indicator of drying endpoint [4]. In Figure 5, the drying end point is where the steepest decrease of AH2 ended and reached the same value as in the preheating phase. The process air relative humidity was difficult to use as an indicator of drying end point of a coated tablet (Figure 6; U1, U2).

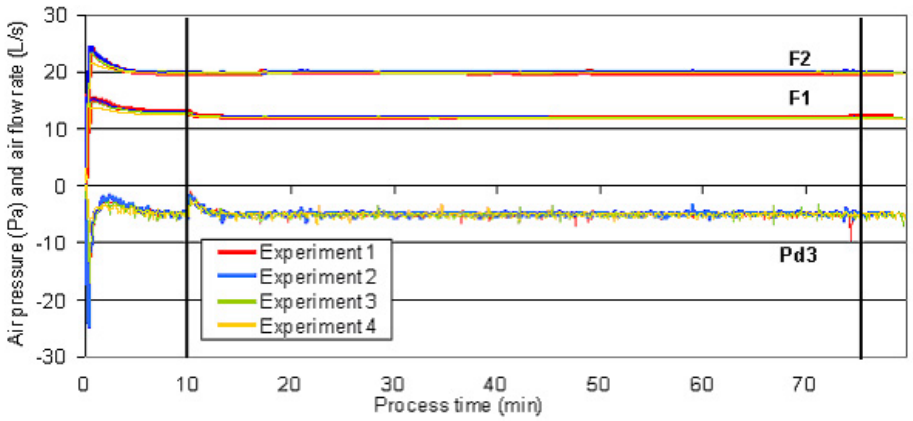

Figure 3. Outlet air flow rate (F2), inlet air flow rate (F1), and negative pan air pressure (Pd3) trendlines of 4 repeat coating experiments during the preheating, spraying, and drying phases of the process.

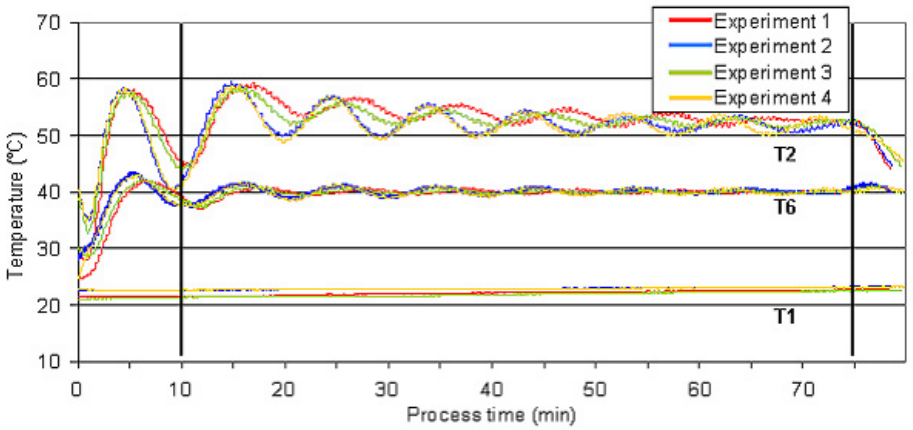

Figure 4. Inlet air temperature (T2, T1) and pan air temperature (T6) trendlines of 4 repeat coating experiments during the preheating, spraying, and drying phases of the process.

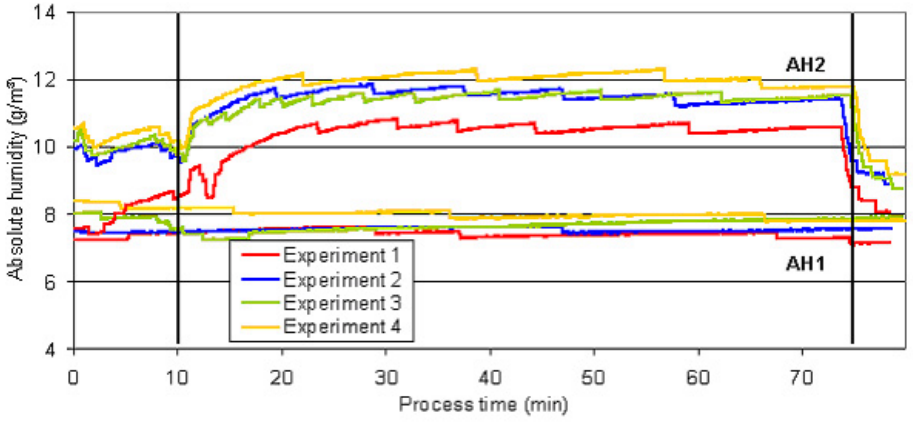

Figure 5. Inlet air absolute humidity (AH1) and outlet air absolute humidity (AH2) trendlines of 4 repeat coating experiments during the preheating, spraying, and drying phases of the process.

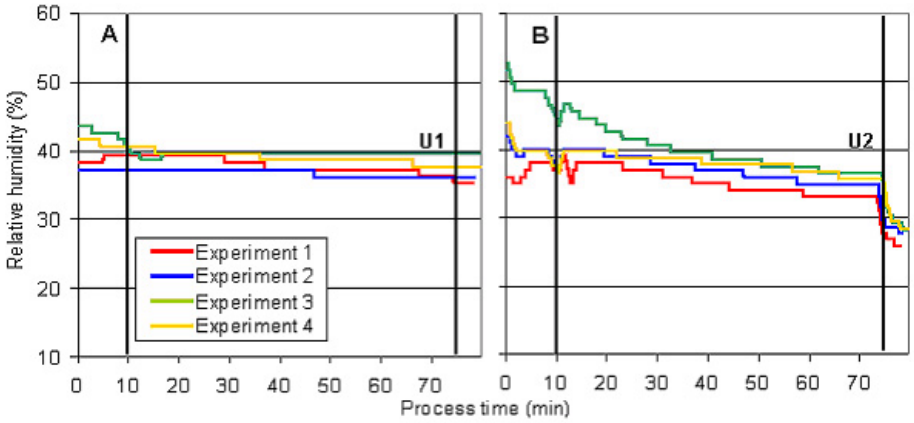

Figure 6. Inlet air relative humidity (A) and outlet air relative humidity (B) trendlines of 4 repeat coating experiments during the preheating, spraying, and drying phases of the process.

Table 3. Responses of the Film Coated Tablets in 4 Repeat Experiments

Repeat experiments	Weight (mg) ± R.S.D. (%) (n=20)	Height (mm) ± R.S.D. (%) (n=20)	Breaking strength (N) ± R.S.D. (%) (n=20)	Roughness (Ra) (μm) ± R.S.D. (%) (n=10)
Experiment 1	505.2±2.7	4.84±1.5	121±11	3.48±15.0
Experiment 2	506.4±2.5	4.86±1.6	119±15	3.58±21.8
Experiment 3	504.9±2.6	4.86±1.8	125±8	3.35±14.6
Experiment 4	504.6±2.5	4.83±1.5	127±8	3.41±21.8

Absolute humidity of the process air was a more reliable indicator of drying end point than relative humidity.

The variation of the evaluated tablet responses in the repeat experiments was negligible (Table 3). The homogeneity and reproducibility of the coating process (ie, batch-to-batch variation) of the repeat experiments are evident also in the behavior of the tablet responses evaluated. On the basis of the measured and monitored process information of the critical process parameters, it can be concluded that the coating process instrumentation and automation worked extremely well.

Influence of process air flow rate on the coating process

Three levels of process inlet air flow rate (F1) and their effects on the behavior of the coating process parameters during different phases of the coating process were observed. With user-controllable outlet air flow rate (F2) values of 12 L/s, 18 L/s, and 24 L/s the corresponding F1 values measured were 6 L/s (minimum), 10 L/s (medium), and 16 L/s (maximum), (Figures 7, 8, and 9, respectively). In Figure 9B, the air flow rates are lower than the set values (Figure 9A) due to the outlet air filter unit (Figure 1) beginning to block up. The outlet air filter unit pressure difference (Pd5) should also be monitored to detect when the filter unit starts to block up.

The process F1 levels affected the inlet air temperature (T2) and the pan air temperature (T6) (Figures 7-9). Sinoidal fluctuation in process air temperatures was caused by the PID controller. At maximum F1 level, T6 and T2 were most linear (T2 50°C-55°C, Figure 9); at medium F1 level, fluctuation in T2 increased (T2 50°C-65°C, Figure 8); and at minimum F1 level, a slight fluctuation in T6 and a much greater fluctuation in T2 (T2 55°C-80°C, 7) were demonstrated. In other words, it is difficult to keep the pan air temperature (T6) constant at low

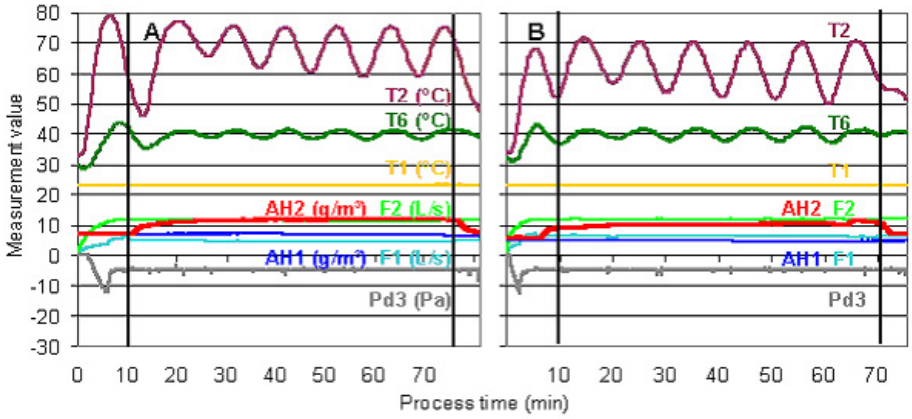

Figure 7. Effects of minimum inlet air flow rate (6 L/s) in 2 coating experiments (A, B). Symbols of the process parameters in Table 1.

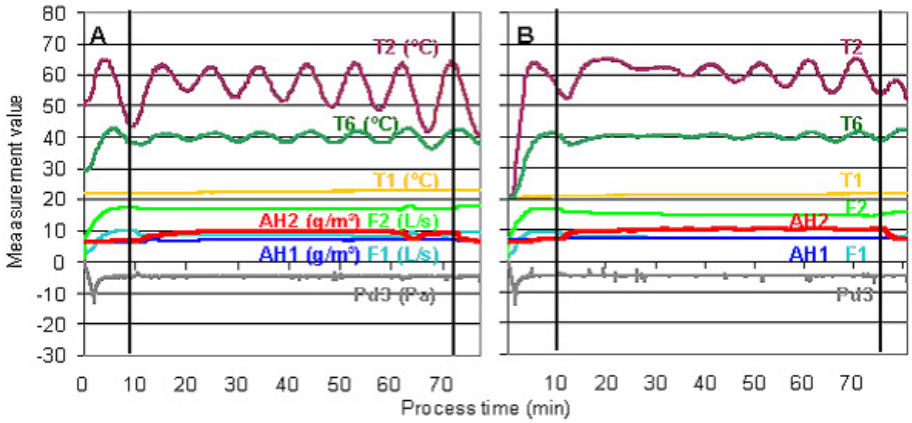

Figure 8. Effects of medium inlet air flow rate (10 L/s) in 2 coating experiments (A, B). Symbols of the process parameters in Table 1.

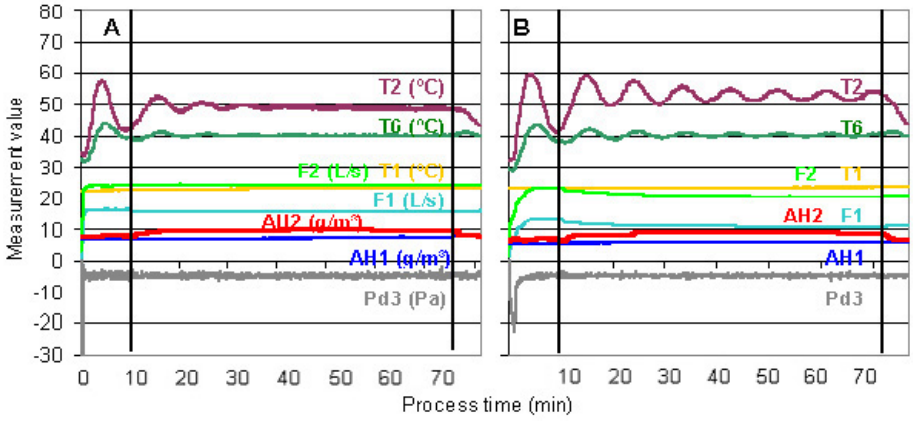

Figure 9. Effects of maximum inlet air flow rate (16 L/s) in 2 coating experiments (A, B). Symbols of the process parameters in Table 1.

Table 4. Loss of Coating Material (n=2) with 3 Inlet Air Flow Rate Levels

Inlet air flow rate (L/s)	Loss of coating material to the filter (%)	Whole loss of coating material (%)
6	3.3	6.0
	3.8	10.7
10	2.3	9.1
	3.8	6.7
16	5.1	23.2
	5.7	28.3

Table 5. Responses of Film-Coated Tablets (n=2) with 3 Inlet Air Flow Rate Levels

Inlet air flow rate (L/s)	Weight (mg) ± R.S.D. (%)(n=20)	Height (mm) ± R.S.D. (%) (n=20)	Breaking strength ± R.S.D. (%) (n=20)	Roughness (Ra) (μm) ± R.S.D. (%) (n=10)
6	503.5±2.6	4.94±5.4	133±7	1.71±12.4
	508.9±2.6	4.86±2.5	127±10	2.00±9.7
10	505.3±2.3	4.91±2.2	133±6	2.53±11.1
	501.9±2.9	4.82±2.5	133±10	2.87±7.8
16	505.6±3.8	4.89±2.1	136±10	4.77±47.0
	508.9±2.5	4.84±1.7	124±13	4.40±39.0

inlet air flow rates (F1) because of the fluctuations demonstrated at low inlet air flow temperatures (T2). An increase in the amount of heat of the incoming process air causes an increase in the tablet bed temperature. These results agree with Franz and Doonan [9] who reported that increasing the inlet air flow rate and temperature and decreasing the spray rate increase the tablet bed temperature.

The process F1 levels affected the absolute humidity of the process outlet air (AH2) (Figures 7-9). During the spraying phase, at the minimum F1 level, AH2 was approximately 5 g/m^3 higher than AH1 (Figures 7). At higher F1 levels, AH2 was approximately 3 g/m^3 higher than AH1 (Figures 8, 9). This increase in AH2 is due to an increased amount of air molecules in proportion to water molecules in the process air. By influencing AH2, F1 also influenced the drying end point. At minimum F1 level, the drying end point was reached later than at higher F1 levels. In other words, drying takes longest at the lowest F1 level.

The process F1 levels caused loss of the coating material (Table 4). When the process air volume increased, the degree of coating material loss also increased. According to a previous study, a large amount of air was drawn into the pan causing displacement of the spray and turbulence within the pan and resulted in poorly coated tablets and a large amount of coating deposited on the pan wall [1]. The coating liquid may dry prematurely in the air stream and be lost in the exhaust air instead of being transferred to the tablets [10]. If the air stream is kept low, the loss of coating material will be negligible [11].

Influence of process air flow rate on the film properties

The inlet air flow rate influenced the coating process, as described above, and the subsequent quality of the coated tablets (Figure 10, Table 5) [1]. With increasing process air volume, the evaporative capacity of the coating process increases and the drying of the tablet surface should become more efficient [9,10]. At maximum F1 level, the surface was rough and uneven, the roughness between tablets varied greatly, and the film quality was considered unacceptable (Figure 10B, Table 5). At high air flow rates, the forming film dries so rapidly that the coating polymer does not coalesce properly and the film deforms. In addition, too rapid drying of the coating liquid spray may make the droplets too vis-

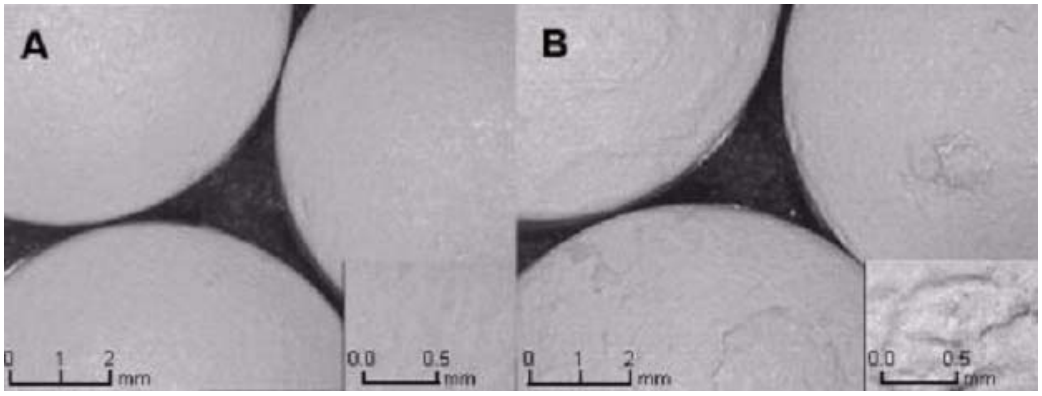

Figure 10. Image analyzer micrographs of the film-coated tablet surface. (A) Minimum inlet air flow rate (6 L/s) and (B) maximum inlet air flow rate (16 L/s).

cous to spread evenly over the tablet surface. At minimum and medium F1 levels, the surface roughness was small, the batches were homogeneous, and the film quality was satisfactory (Figure 10A, Table 5). At a low air flow rate, the drying was slower and the film formed properly. The effects of F1 levels on the other tablet responses evaluated (weight, height, and breaking strength) were negligible (Table 5).

The process air flow rate was found to be a critical process parameter that is important to control and measure. The air flow rate measurement system helps to determine the optimal air flow rate with regard to film drying and quality.

CONCLUSIONS

The major operational coating process parameters related to film coating in a perforated pan-type coater can be measured and monitored continuously with the instrumentation system described in this paper. A novel inlet and outlet air flow rate measurement system was developed and proven reliable in use. The process automation worked well and provided comprehensive data of each coating experiment. The reproducibility of the coating processes using the instrumented system was good. The inlet air flow rate influenced the coating process, especially the drying of the tablet surface and thereby the quality of the tablets, and the loss of coating material. A fully automated system and historical data storage of critical process parameters provide an excellent tool for controlling, analyzing, and characterizing the film coating process.

Process automation and monitoring of critical process parameters can be used to increase the overall process efficiency and predictability and to improve the homogeneity and the reproducibility of the tablet batches. This will ensure the high quality and safety of the final coated products, which are mandatory requirements of tablet manufacturing.

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REFERENCES

1. Cole GC, May G, Neale PJ, Olver MC, Ridgway K. The design and performance of an instrumentation system for aqueous film coating in an industrial tablet coating machine. Drug Dev Ind Pharm. 1983;9(6):909-944.

2. Le Floc'h JY. Automation of aqueous film coating. Drug Dev Ind Pharm. 1996;22(1):45-50.

3. Yoakam DA, Campbell RJ. Modeling of a film coating system for computer automation. Pharm Technol. 1984;8(Jan):38-44.

4. Rantanen J, Känsäkoski M, Suhonen J, Tenhunen J, Lehtonen S, Rajalahti T, Mannermaa J-P, Yliruusi J. Next generation fluidized bed granulator automation. Pharm Sci Tech. 2000;1(2) article 10.

5. UBM Messtechnik GmbH. Microfocus Non-contacting Measurements [brochure], Ettlingen, Germany: UBM Mebtechnik GmbH; 1995.

6. UBM Messtechnik GmbH. UBM System Reference Guide, UBM Measurement and Analysis Software for Windows, Rev 1.3. Ettlingen, Germany:UBM Mebtechnik GmbH; 1996.

7. Riippi M, Antikainen O, Niskanen T, Yliruusi J. The effect of compression force on surface structure, crushing strength, friability and disintegration time of erythromycin acistrate tablets. Eur J Pharm Biopharm. 1998;46:339-345.

8. Okutgen E, Jordan M, Hogan JE, Aulton ME. Effects of tablet core dimensional instability of the generation of internal stresses within film coats. Part II: temperature and relative humidity variation within a tablet bed during aqueous film coating in an accela-cota. Drug Dev Ind Pharm. 1991;17(9):1191-1199.

9. Franz RM, Doonan GW. Measuring the surface temperature of tablet beds using infrared thermometry. Pharm Technol. 1983;7(Mar):55-67.

10. Porter SC, Verseput RP, Cunningham CR. Process optimization using design of experiments. Pharm Technol. 1997;21(Oct):60-70.

11. Schmidt PC, Niemann F. The MiniWid-coater: I. Design and evaluation of a temperature-controlled miniature fluid-bed pan coater. Drug Dev Ind Pharm. 1992;18(17):1907-1919.