Mathematical Modeling of an Aqueous Film Coating Process in a Bohle Lab-Coater: Part 2: Application of the Model

Submitted: August 24, 2005; Accepted: March 22, 2006; Published: May 5, 2006

Susanne Page,[1] Karl-Heinrich Baumann,[2] and Peter Kleinebudde[3]

[1]Martin-Luther-University Halle-Wittenberg, Institute of Pharmaceutics and Biopharmaceutics, Wolfgang-Langenbeck-Str 4, D-06120 Halle, Germany. Current address: F. Hoffmann-La Roche Ltd, Basel, Switzerland
[2]Martin-Luther-University Halle-Wittenberg, Department of Engineering, Geusaer Str 132, D-06217 Merseburg, Germany
[3]Heinrich-Heine-University Duesseldorf, Institute of Pharmaceutics and Biopharmaceutics, Universitaetsstr 1, 40627 Düsseldorf, Germany

ABSTRACT

For the prediction of the air and product temperatures, the product moisture, and the air humidity during a coating process in a Bohle Lab-Coater, a model was developed. The purpose of this work was to determine the limit moisture, the critical moisture, and the constant for the exchange rate between both zones and to use these values for other sets of experiments to test the model. The adaptation of the 3 parameters (limit moisture, critical moisture, and exchange rate constant) was done by calculation of the product temperature in both zones for several sets of parameters in order to minimize the sum of square deviation between the calculated and the measured product temperatures. This set of parameters was used to test the validity of the model. By applying the model, the product temperature could be predicted based on the product, process, and equipment-related parameters. Hence, the model can be used to theoretically investigate the influence of different process parameters. The mean difference between the predicted and measured product temperatures in the steady state is ~2 up to 3 K using the determined parameter set for the limit moisture, the critical moisture, and the exchange rate constant. The model is useful for the prediction of the air and product temperatures, the product moisture, and air humidity during a coating process in the Bohle Lab-Coater using round, biconvex tablets.

KEYWORDS: film coating, mathematical modeling, heat and mass transfer, convection, particle movement.

INTRODUCTION

In Part 1 of this article, a mathematical model based on balance equations was developed describing the change of air humidity, product moisture, enthalpy of air, and the product. Owing to experimental limitations, 3 parameters, which are required for the calculation, could not be determined directly. These are

- the constant c_{ψ_2} for the calculation of the exchange rate ψ_2 and
- the critical moisture x_k in kg/kg and the limit moisture x_G in kg/kg.

Indeed, they will be determined by adaptation of a set of experiments. From the examination of the temperature difference[1] during earlier investigations of the mixing behavior, the mathematical correlation between the difference of the product bed temperatures in the 2 zones and the spray rate, the pan speed, and inclination of the axis of rotation are well known. But not only has the temperature difference depended on the investigated process parameters, in fact the product temperature itself depended on the measuring position in the tablet bed. These results correspond with the results found by Okutgen et al in the Accela Cota.[2] The second part of the article describes the determination of c_{ψ_2} (constant for the exchange rate), x_k (critical moisture), and x_G (limit moisture) and describes experiments to check the model with respect to the accuracy of prediction.

Corresponding Author: Peter Kleinebudde, Heinrich-Heine-University Duesseldorf, Institute of Pharmaceutics and Biopharmaceutics, Universitaetsstr 1, 40627 Düsseldorf, Germany. Tel: +49 211 811 4220; Fax: +49 211 811 4251; E-mail: Kleinebudde@uni-duesseldorf.de

MATERIALS AND METHODS

Materials

For the measurement of the product temperature in the spray zone and drying zone dependent on other coating process parameters, enteric-coated, round, biconvex tablets with a diameter of 11 mm, respectively, 8 mm were used. The film coating (~5 mg dry polymer/cm^2) contained the polymer Eudragit L30D55. Detailed information regarding the shape, amount, and dimensions of the tablets can be found in Tables 1 and 2.

Equipment

For the experiments, a Bohle Lab-Coater BLC5 was used. The coater is described in more detail in part 1. The dimensions of the drum and some key information with respect to the mixing ribbons are listed in Table 3.

Table 1. Product-specific and Process-related Parameters for the Modeling

Properties of the Product (round, biconvex tablets)			
Diameter d		11 mm	
Tablet mass M_{tablet}		460 mg	
Base height s		2 mm	
Batch size $M_{tP1}+M_{tP2}$		5 kg	
Callotte height h		1.5 mm	
Bulk density of the tablets ρ_{bulk}		638.9 g/L	
Parameter of the Process			
Spraying liquid		Demineralized water	
Inlet air temperature T_{AirI}		50°C (directly at the entrance 46°C)	
Air flow rate V_N		120 Nm^3/h	
Exchange rate φ_2		$0.12431 \cdot c_{\varphi 2} \cdot n$	
At an inclination of	−2.2°	1.0°	4.2°
Mass of tablets in zone 1 M_{tP1}	2.38 kg	2.55 kg	2.72 kg
Mass of air in zone 1 M_{tL1}	0.0117 kg	0.0114 kg	0.0111 kg
Mass of air in zone 2 M_{tL2}	0.0113 kg	0.0116 kg	0.0119 kg
Values for the Starting Point t = 0			
Moisture of the product X_j		0.059 kg/kg	
Temperature of the product T_{Pj}		individual	
Humidity of the air Y_j		0.004 kg/kg	
Temperature of the air T_{Airj}		30°C	

Methods

Determination of the product temperatures dependent on different process parameters

Two temperature sensors (PT-100) were calibrated in the range from 0°C to 90°C and installed in the drum in order to measure the product (tablet bed) temperature in the drying zone and in the spray zone. The distance between the front panel and the temperature sensor in the spraying zone was 90 mm; between the front panel and the spray nozzle, 160 mm; and between both sensors, 300 mm. The position of the sensors was determined visually prior to the next experiment.

In order to avoid a coating of the PT100-sensors, especially in the spray zone, the coating trials were simulated by spraying water onto the enteric-coated tablets. For the trials, which were used for the adaptation of the model by parameter

Table 2. Product-specific and Process-specific Parameters for the 8-mm Tablets (Plan A)

Properties of the Product (round, biconvex tablets)			
Diameter d		8 mm	
Tablet mass M_{tablet}		185 mg	
Base height s		2 mm	
Batch size $M_{tP1}+M_{tP2}$		3.75 kg	
Callotte height h		0.75 mm	
Bulk density of the tablets ρ_{bulk}		812.2 g/L	
Parameter of the Process			
Spraying liquid		Demineralized water	
Inlet air temperature T_{AirI}		70°C (directly at the entrance 56°C)	
Air flow rate V_N		68 Nm^3/h	
Exchange rate φ_2		$0.1036 \cdot c_{\varphi 2} \cdot n$	
At an inclination of	0°	2°	4°
Mass of tablets in zone 1 M_{tP1}	1.875 kg	1.993 kg	2.111 kg
Mass of air in zone 1 M_{tL1}	0.0130 kg	0.0128 kg	0.0126 kg
Mass of air in zone 2 M_{tL2}	0.0130 kg	0.0132 kg	0.0134 kg
Values for the Starting Point t = 0			
Moisture of the product X_j		0.059 kg/kg	
Temperature of the product T_{Pj}		individual	
Humidity of the air Y_j		0.0033 kg/kg	
Temperature of the air T_{Airj}		40°C	

Table 3. Equipment-related Parameters for the Bohle Lab-Coater BLC 5

Properties of the Drum	
Diameter D	316 mm
Cylindrical part H	356 mm
Air inlet $A_{inlet\ air}$	0.165 × 0.110 m^2
Height of outer ribbon h_{out}	15 mm
Height of inner ribbon h_{in}	15 mm
Height of h_{base}	20 mm

optimization, the enteric-coated tablets with a diameter of 11 mm were used. The product temperature in both zones was measured dependent on the process parameters, whereas for this set of experiments all parameters except the spray rate, the inclination of the drum, and the pan speed were kept constant. The spray rate was in the range of 5 to 21 g/min, the inclination of the drum was in the range of −2.2° to 4.2°, and the pan speed varied between 5 and 35 rpm.

For all other trials, enteric-coated tablets with a diameter of 8 mm were used. The product temperature in both zones was measured dependent on the process parameters. In plan A all process parameters except the pan speed and the inclination of the drum were kept constant. The inclination of the drum was in the range from 0° to 4° and the pan speed varied between 6 and 32 rpm. In the second set of trials with the 8-mm enteric-coated tablets (Plan B), the influence of the air flow rate (58 to 78 Nm^3/h) and the spray rate (7 to 13 g/min) were investigated.

Determination of the specific heat capacity of the product (tablets)

The specific heat capacity of the tablets was determined according to DIN 51007. For the determination, a differential scanning calorimeter DSC 820 (Mettler Toledo GmbH, Giessen, Germany) was used. The nitrogen flow was set to 80 mL/min, and the specific heat capacity was investigated in the temperature range from 0°C to 100°C. The sample (20 mg prepared by milling of the tablets in a mortar) were weighed into the aluminum pans and hermetically sealed. The heating rate was 10 K/min. All measurements were performed with baseline correction. For the determination of the specific heat capacity, the second heating cycle was used because an endothermic peak was visible in the first heating cycle. Sapphire was used as reference material. The functional correlation between the specific heat capacity and the temperature can be described by a polynomial of third degree. The corresponding equations are Equation 2 for the 11-mm tablets and Equation 3 for the 8-mm tablets.

Determination of the temperature at the entrance of the drum (effective inlet air temperature)

In the model equations, the temperature direct at the entrance is used. Owing to heat loss, this temperature is normally lower than the inlet air temperature. For the determination of the effective inlet air temperature, the flexible inlet tube was removed from the drum, and at the open end a calibrated thermometer (Type MD 3040, Beckmann and Egle Industrie

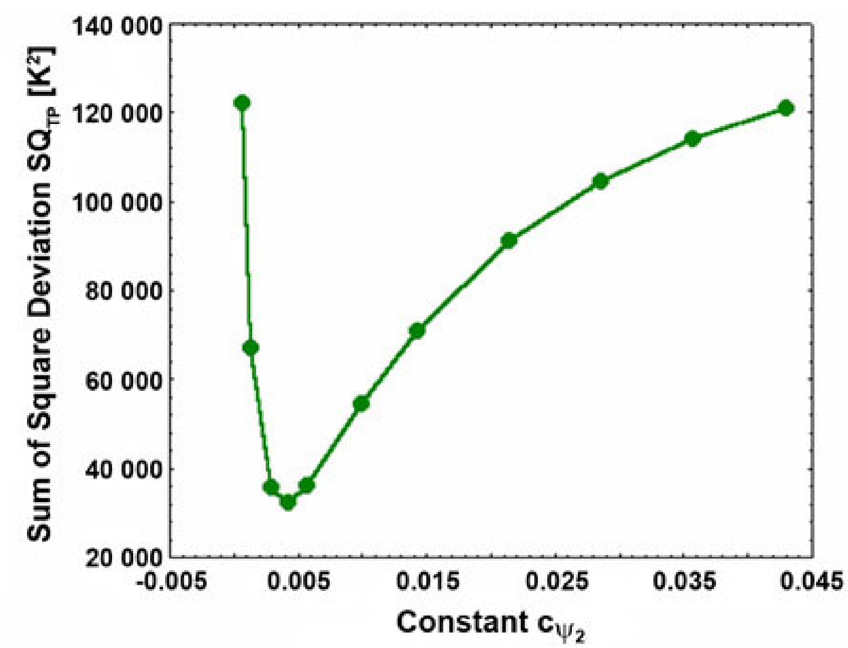

Figure 1. Connection between the sum of the square deviation and the constant c_{ψ_2} for calculating ψ_2 for $x_G = 0.045\ kg/kg$ and $x_k = 0.12\ kg/kg$.

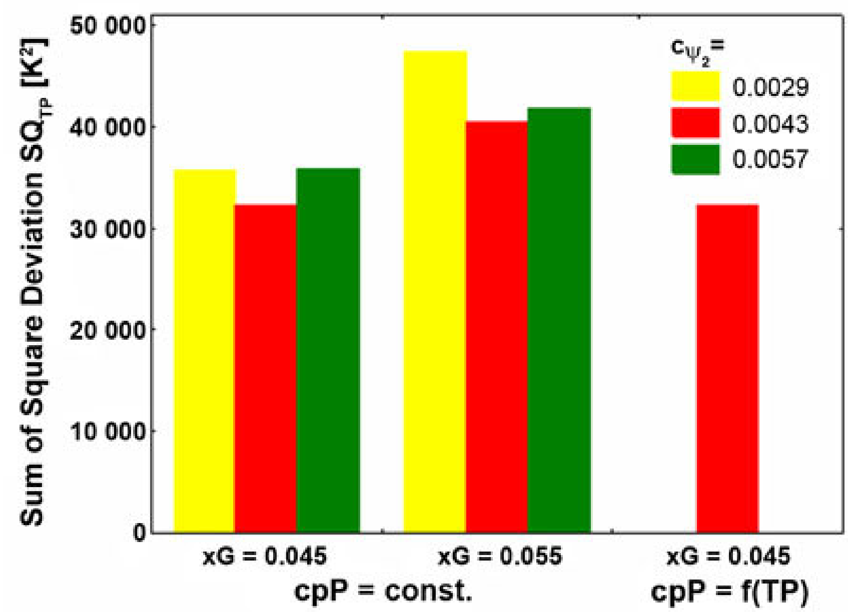

Figure 2. Connection between the sum of the square deviation the constant c_{ψ_2} and the limit moisture x_G *for* $x_k = 0.12\ kg/kg$.

Elektronic GmbH, Kernen, Germany) was installed. The effective inlet air temperature was determined in dependence of the air flow rate (20 to 180 Nm^3/h in steps of 40 Nm^3/h) and the inlet air temperature (30°C to 80°C in steps of 10 K).

Numerical solution of ordinary differential equations

The ordinary differential equations (ODEs) were solved using the Runge-Kutta-Fehlberg method implemented in Maple 6 (Maplesoft, Waterloo, Ontario, Canada). The function dsolve (Maple 6) used a dynamic integration step width, where the maximum number of steps chosen was 3000.

RESULTS AND DISCUSSION

Adaptation of the Model by Parameter Optimization

As already mentioned, some of the parameters used in the model equations (see Part 1) have to be determined in the coating pan itself. This is because these parameters depend on the material to coat, and the hydrodynamic conditions in the coating process. At the moment, appropriate devices are not available to determine them separately. Therefore they have to be determined by adaptation of a set of experiments. The following parameters have to be determined in this way:

- the constant c_{ψ_2} for the calculation of the exchange rate ψ_2,
- the critical moisture x_k, and
- the limit moisture x_G.

Herein, the critical moisture indicates the transition from the first to the second drying section, whereas the limit moisture describes the moisture at the end of the second drying section. The last 2 parameters depend mainly on the drying conditions.

For the calculations, the experiments described in an earlier work were used.[1] An adaptation between the calculations of a set of the 3 parameters and the experimental values was performed by minimizing the sum of square deviation between calculated and measured tablet bed temperature in

Table 4. Comparison Between the Calculated and Measured Temperatures

Pan Speed [rpm]	Inclination [°]	Spray Rate [g/min]	T_{P1} [°C]	T_{P1calc} [°C]	$\lvert\Delta T_{P1}\rvert$ [K]	T_{P2} [°C]	T_{P2calc} [°C]	$\lvert\Delta T_{P2}\rvert$ [K]
20	1.0	13	30.2	31.7	1.5	37.9	37.3	0.6
5	1.0	13	26.3	30.5	4.2	41.3	42.0	0.7
35	1.0	13	31.1	32.1	1.0	33.9	35.6	1.7
20	−2.2	13	29.9	31.7	1.8	33.9	37.0	3.1
20	4.2	13	31.0	31.7	0.7	34.5	37.6	3.1
20	1.0	5	39.1	40.4	1.3	43.0	42.8	0.2
20	1.0	21	22.9	23.3	0.4	31.3	30.4	0.9

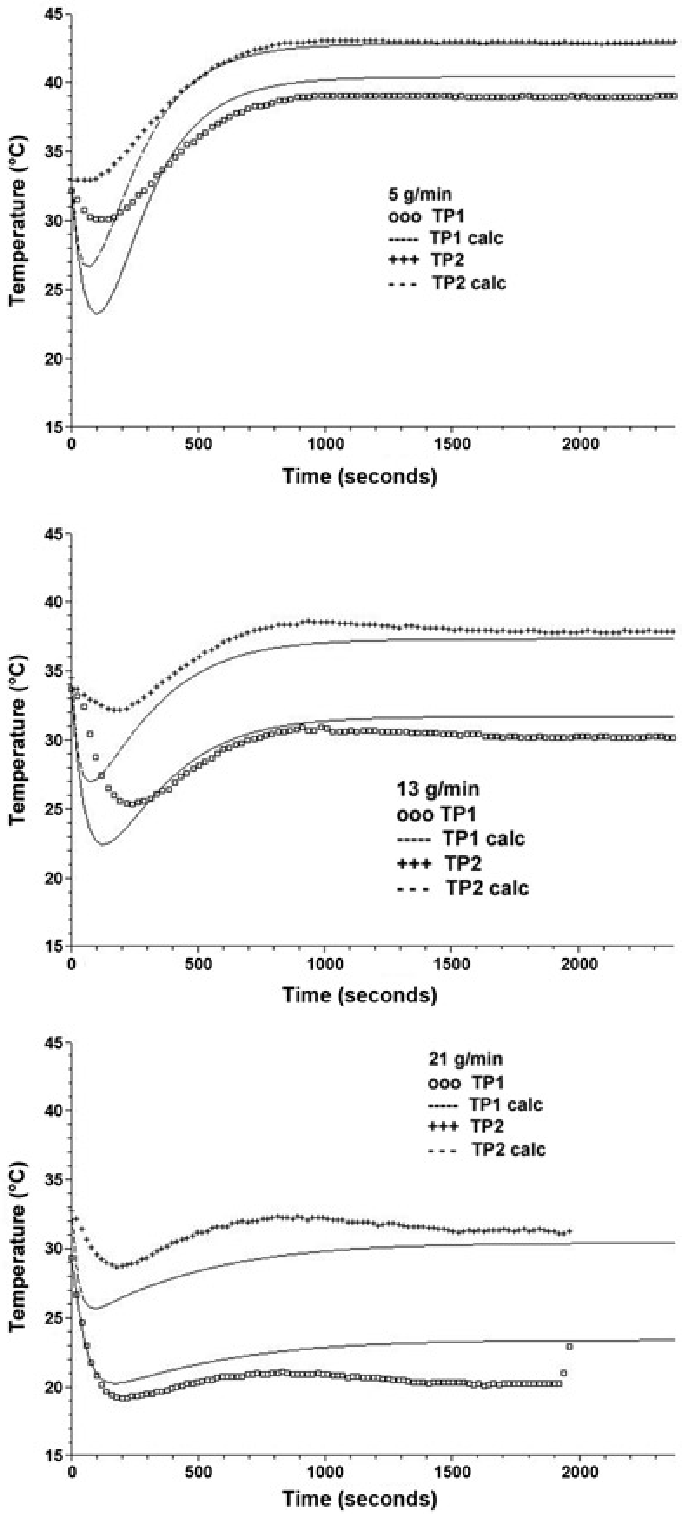

Figure 3. Temperature curves for an inclination of 1° and a pan speed of 20 rpm.

both zones (100 points per zone). The sum of the square deviation for n points per zone can be calculated according to the following equation:

$$SQ_{T_p} = \sum_{i=1}^{n} \left\{ \left[T_{p1_{calc}}(i) - T_{p1}(i) \right]^2 + \left[T_{p2_{calc}}(i) - T_{p2}(i) \right]^2 \right\}, \qquad (1)$$

with $T_{P_{calc}}(i)$ as calculated product temperature (1 = spray zone, 2 = drying zone) at time point *i* and $T_P(i)$ as measured product temperature (1 = spray zone, 2 = drying zone) at time point *i*. The equipment-related parameters, the product-specific parameters, and the process parameters of the experiments used for the adaptation are given in

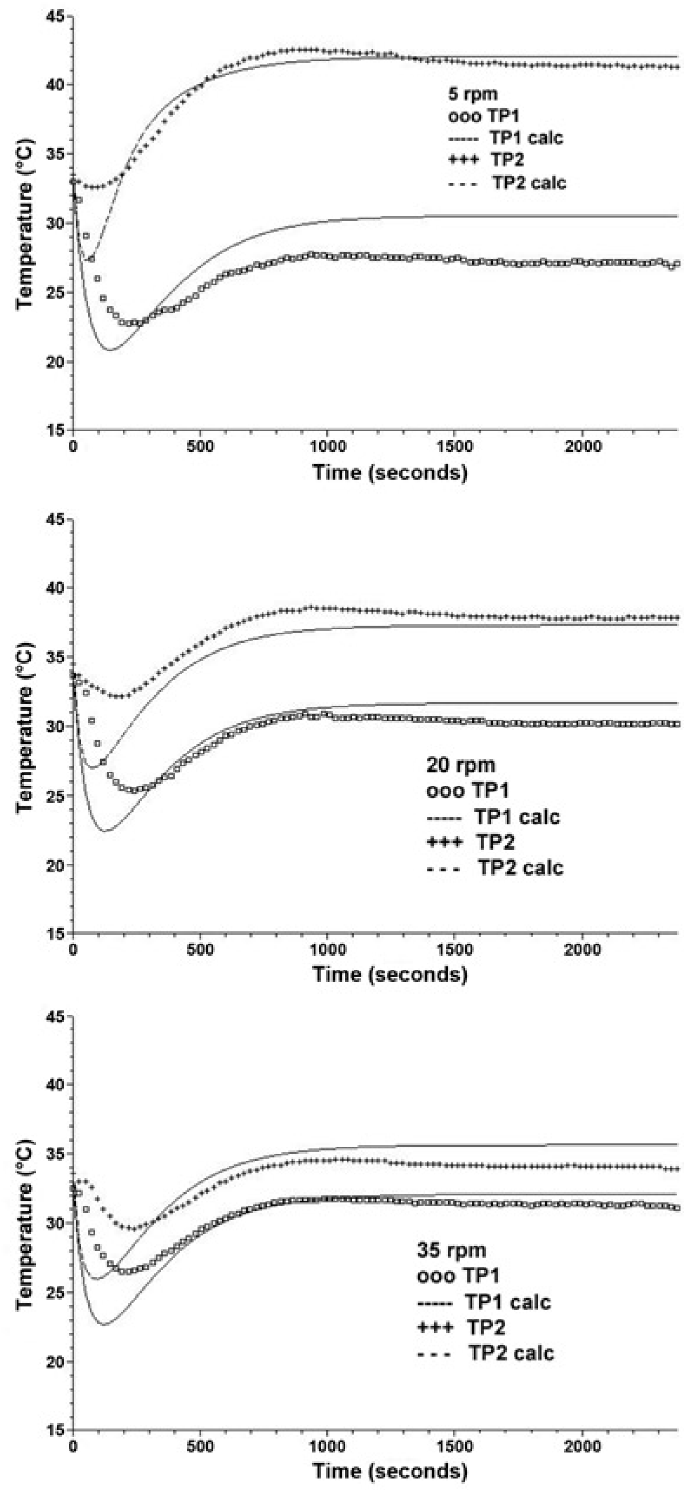

Figure 4. Temperature curves for an inclination of 1° and a spray rate of 13 g/min.

Tables 1 and 3. The inclination of the drum, the pan speed, and the spray rate were variables in the study. The individually measured tablet bed temperatures at $t = 0$ were used as start temperature.

The temperature-dependent specific heat capacity of the tablets could be calculated according to Equation 2.

$$c_{p\,P}\left[\frac{J}{kgK}\right] = 1153.4 + 7.0293T_P - 0.0375T_P^2 + 2{\cdot}10^{-4}T_P^3 \quad (2)$$

From the adaptation using the sum of square deviation between the calculated and measured temperatures (for a constant heat capacity of the tablets), the following set of parameters was derived: for the critical moisture, $x_k = 0.12\ kg/kg$; for the limit moisture, $x_G = 0.045\ kg/kg$; and for the exchange rate, $\psi_2 = 0.0043 \cdot 0.12431\ n$. The sum of square deviation is for all 28 experiments, and for this set of parameters $SQ_{T_P} = 32238\ K^2$, this is equal to a mean temperature difference ΔT per point of 2.4 K. In Figure 1, the connection between the sum of the square deviation and the constant c_{ψ_2} for calculating ψ_2 is given. A minimum could be observed at $c_{\psi_2} = 0.0043$. In Figure 2, the connection between the limit moisture x_G, the constant c_{ψ_2}, and the sum of square deviation is given. An increase of x_G leads to an increase of the sum of square deviation up to a value of $SQ_{T_P} = 40429\ K^2$, which corresponds to a temperature difference ΔT per point of 2.7 K. The same figure also shows that taking the temperature-dependent heat capacity into account (Equation 2) does not make so much progress. In that case, SQ_{T_P} decreased to 32185 K^2. Nevertheless, the temperature-dependent specific heat capacity of the product (tablets) was used for further calculations.

By means of some examples from the series of experiments in which the temperature difference was evaluated in dependence of the same process parameters[1] the goodness of adaptation with the 3 evaluated parameters and by considering the temperature-dependent heat capacity of the tablets should be demonstrated. Criteria are the sum of square deviation of the temperatures over the whole process as well as the temperature difference between the calculated and measured temperatures in the steady state, characterized at the end point of the process. Table 4 displays the measured and calculated temperatures for some experiments as well as the temperature difference. In the first row, the center point of the experimental plan is given. The goodness of adaptation is satisfactory under the following constraints: that the measured values could be incorrect owing to the margin of error of the equipment (PT-100-sensors 1 K) and that no heat loss is included in the model.

The measured and calculated temperature curves during the process are shown in Figure 3 as a function of the spray rate. Figure 4 shows the temperature curves dependent on the pan speed. The diagrams show a good conformity between the measured and calculated temperatures during the steady state and a fair conformity over the whole process.

The evaluated adaptation parameters should be tested in the next step with other experimental conditions. For this purpose experiments are suitable where tablets with other properties, another inlet air temperature, or different air flows were used. Therefore it must be taken into account that changing the drying conditions can lead to a slight change of the parameters, limit moisture and critical moisture.

Modeling for Round, Biconvex Tablets

In the previous section, the adaptation parameters were found. Theses parameters were tested using the results of 2 experimental plans (plans A and B) with round, biconvex tablets with a diameter of 8 mm. The properties of the tablets are described in Table 2. The heat capacity in dependence of the temperature for these tablets is

$$c_{pP}\left[\frac{J}{kgK}\right] = 1072 + 6.1249T_P - 0.0393T_P^2 + 3{\cdot}10^{-4}T_P^3 \quad (3)$$

In the first experimental design (Plan A), the correlation between the tablet bed temperatures in the spray and drying

Table 5. Comparison Between the Calculated and Measured Temperatures for the 8-mm Tablets (Plan A)

Pan Speed [rpm]	Inclination [°]	T_{P1} [°C]	T_{P1calc} [°C]	$\|\Delta T_{P1}\|$ [K]	T_{P2} [°C]	T_{P2calc} [°C]	$\|\Delta T_{P2}\|$ [K]
6	0	36.2	36.5	0.3	45.4	49.6	4.2
6	2	35.0	37.1	2.1	44.7	50.1	5.4
6	4	38.2	36.9	1.3	46.6	50.3	3.7
19	0	35.1	37.5	2.4	40.7	44.5	3.8
19	2	37.2	37.5	0.3	42.2	44.9	2.7
19	4	37.2	37.7	0.5	41.9	45.3	3.4
32	0	36.6	38.1	1.5	40.7	42.7	2.0
32	2	38.1	38.0	0.1	42.0	42.9	0.9
32	4	36.8	38.1	1.3	40.8	43.3	2.5

zones and the pan speed, as well as the inclination of the axis of rotation, was studied. The coating step was simulated by spraying water onto enteric-coated tablets. The temperatures in the tablet bed (in both zones) were measured during the whole process and were used to compare the calculated temperatures with the measured temperatures. The process parameters of this set of experiments and the starting values are shown in Table 2.

The values at a temperature of 40°C were used in the equations for the heat capacity of the air, water vapor, and water. The heat capacity of the tablets is already given in Equation 3.

First, calculations using the parameters investigated by the adaptation showed, for the 12 experiments with 80 point per temperature each, that the sum of square deviation is $SQ_{T_P} = 63685\ K^2$; this is equal to a mean temperature difference of $5.8\ K$ per point. This finding also means that the prediction of the model is not satisfactory with the parameters derived by adaptation (see Adaptation of the Model by Parameter Optimization). A psureossible reason for this is a change in the drying conditions (inlet air temperature and air flow). The calculations for the temperature progress were repeated with a limit moisture of $x_G = 0.055 kg/kg$. This value resulted in a slightly worse adaptation (mean temperature deviation of $2.7\ K$ instead of $2.4\ K$) for the test data set for parameter adaptation compared with a limit moisture x_G of $0.0450\ kg/kg$. In the actual case, the sum of square deviation decreased to $46840\ K^2$. This correlates to a temperature difference of $2.96\ K$ per point, which is comparable with the calculations (parameter adaptation). The calculated and measured temperatures for a limit moisture of $0.055\ kg/kg$ is shown in Table 5. The center point of the experimental plan was evaluated 4 times.

On closer examination of the temperature at the end point, which also characterized the steady-state, the calculated temperatures in the spray zone as well as in the drying zone are higher compared with the measured temperatures. The heat loss over the wall of the drum, which is not included in the model so far, is responsible for this result.

In a second series of experiments (plan B) the air flow rate and spray rate were varied at a constant pan speed of $19\ rpm$ and an inclination of 2°. The air flow rate was varied between 58 and 78 Nm^3/h and the spray rate between 7 and 13 g/min. All other process parameters remained unchanged (Table 2). At the starting point, only the air humidity changed to $0.0062\ kg/kg$. The calculations were performed using the adaptation parameters mentioned above. At a limit moisture x_G of $0.045\ kg/kg$, the total deviation SQ_{T_P} is $67565\ K^2$, which corresponds to a mean difference per point of $5.9\ K$. Using a limit moisture value of $0.055\ kg/kg$, the prediction of the model improves. In that case the total deviation over all points is $12947\ K^2$, which is equal to a mean difference of $2.6\ K$ per point, comparable with the adaptation calculations. Figure 5

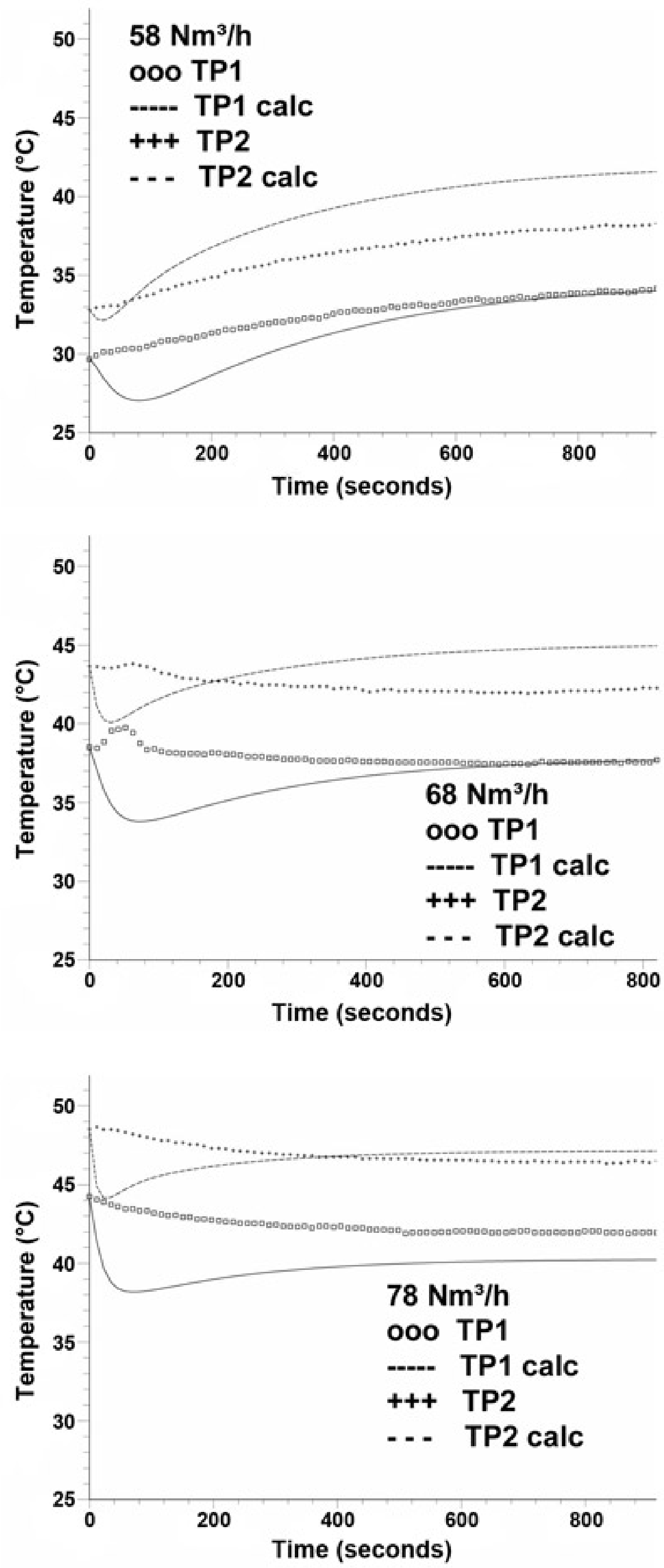

Figure 5. Temperature curves for a spray rate of 10 g/min.

Table 6. Comparison Between the Calculated and Measured Temperatures for the 8-mm Tablets (Plan B)

Air Flow [Nm^3/h]	Spray Rate [g/min]	T_{P1} [°C]	T_{P1calc} [°C]	$\|\Delta T_{P1}\|$ [K]	T_{P2} [°C]	T_{P2calc} [°C]	$\|\Delta T_{P2}\|$ [K]
58	7	39.3	40.9	1.6	44.0	46.4	2.4
58	10	34.2	34.0	0.2	38.3	41.6	3.3
58	13	29.3	28.4	0.9	32.4	37.1	4.7
68	7	42.0	42.9	0.9	46.7	48.2	1.5
68	10	37.7	37.7	0	42.3	44.9	2.6
68	13	34.1	32.5	1.6	38.6	41.4	2.8
78	7	43.9	44.8	0.9	48.2	49.7	1.5
78	10	41.9	40.2	1.7	46.5	47.1	0.6
78	13	35.2	35.6	0.4	40.0	44.3	4.3

shows some of the measured and calculated temperature curves, where the air flow rate varied between 58 and 78 $Nm\,^3/h$. With respect to the goodness of prediction, there are only slight differences between the measured and predicted temperatures during the steady state. Table 6 shows the measured and predicted temperatures at the end point.

The observation made in the other experiments could also be applied here. The predicted temperatures in the drying zone are always higher compared with the values derived from the measurement. The reason is the heat loss over the wall of the drum as already explained. By the virtue of that phenomenon, the predictions of the tablet bed temperatures with the adaptation parameters $x_G = 0.055\ kg/kg$, $x_k = 0.12\ kg/kg$, and $c_{\psi_2} = 0.0043$ are quite good.

Owing to the precision of measurements of PT-100 sensors, which is ±1 K, the difficulty in measuring in a 2-phase system, and the facts that the heat loss was not taken into account and only 3 material constants were used for a wide variety of coating conditions, a difference between the calculated and measured temperatures of 2 to 3 K is a very good result. In most cases, the predicted temperatures derived from the model calculations were slightly higher than the measured temperatures. The reason for this result is the heat loss over the drum wall, which was not taken into account in the current study. To integrate the heat loss in the model, different heat transfers at 3 surfaces would have to be considered. These are the heat transfer from the product to the wall of the drum, between the process air and the drum, and between the wall of the drum and the surrounding. A heat transfer between 2 surfaces can be calculated as the product from the heat transfer coefficient, the surface, and the temperature difference. The heat transfer coefficient is unknown for this case and cannot be derived easily.

CONCLUSION

In the present stage, the model can be used to predict the correlation between different process parameters and the temperatures in the spray and drying zones in the Bohle Lab-Coater BLC 5. The model can be used as a tool to optimize a coating process by predicting the steady-state temperatures in the 2 zones of the coater as a result of the settings of the process parameters. One application might be the calculation of the optimal spray rate without dropping below a required product temperature.

ACKNOWLEDGMENTS

The authors would like to thank the company L. B. Bohle for the opportunity to work with the Bohle Lab-Coater BLC 5. We also thank Dr. Thomas Lüpke for the determination of the specific heat capacity of the tablets. The cores were kindly provided by Arzneimittelwerk Dresden GmbH, Radebeul, Germany, and Rottendorf, Ennigerloh, Germany.

REFERENCES

1. Tobiska S, Kleinebudde P. A simple method for evaluating the mixing efficiency of a new type of pan coater. *Int J Pharm.* 2001;224:141–149.

2. Okutgen E, Jordan M, Hogan JE, Aulton ME. Effects of tablet core dimensional instability on 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;17:1191–1199.