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A simple method for evaluating the mixing efficiency of a new type of pan coater

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Abstract

The objective of this study was to investigate some important process parameters on the mixing behavior of a new coater type. The coater used in this study, the Bohle BLC pan coater, differs from other coaters in its high length to diameter ratio. The pan coater can be divided into two zones: drying and spraying zone. The temperature difference between two points in the pan (one in each zone) was used to explore the influence of some process parameters, i.e. the pan speed and the inclination of the rotation axis on the mixing behavior. In addition, the effect of the spray rate on the temperature difference was studied. The results of the current study demonstrated the possibility to characterize the mixing behavior in a pan coater by a simple temperature measurement. The temperature difference method resulted in a model, which was comparable to the model from a conventional mixture experiment. It was shown that the pan speed and the spray rate influenced the temperature difference and, consequently, the mixing efficiency. However, the inclination of the rotation axis did not show an important effect. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Pan coater; Mixing efficiency; Temperature; Pan speed; Spray rate; Inclination of the rotation axis

1. Introduction

Pharmaceutical coating, e.g. enteric or sustained release coating, is often used to produce tablets with desired properties. So, it is very important to maintain the consistency of the coating process in order to avoid any dissatisfactory deviation in the properties or the produced tablets. As mixing during the coating process greatly influences the batch homogeneity, it is important to explore the effect of the various factors involved in the mixing process in the pan coater.

The mixing is a crucial pharmaceutical operation, which is considered as a quality control parameter, and can greatly influence the homogeneity of the resulted coating film and, consequently, this affects the properties of the produced tablets. Low enteric coating will result in tablets with insufficient protection for the acid-labile

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drug against the gastric fluids, whereas tablets with excess coating will not dissolve within the required time. Therefore, many authors have investigated the effect of different factors, such as the pan speed, the tablet shape and the arrangement of the baffles, on the inter-unit uniformity.

Ridgway and Segovia (1968) described the mechanism of particle motion in a rotary coating pan with the coefficient of self-diffusion. For this purpose they used three different methods: linear sampling, total compartmenting of the bed and high-speed cinéphotography. Shinbrot et al. (1999) used another type of total compartmenting to investigate the mixing of granular solids in cylindrical vessels. They used small glass beads with different colors which were mixed for a certain time. After the vessel was stopped, the mixture was frozen by infiltrating it with methacrylat copolymer. Then the solidified, preconserved mixture was sliced to reveal the internal mixing patterns. This technique allows a direct and continuous observation of the mixture structure. They applied these experiments to a mathematical model in order to describe the spontaneous chaotic granular mixing.

Bauer (1977) investigated the mixing effect in rotary vessels by observing the movements of the rotating material in transparent rotary model-apparatus from different angles. The motion of the particles was recorded photographically and cinematographically. It has been shown that the shape of the vessel, the inclination of the rotation axis and the filling degree of the vessel are important factors during the mixing process.

Leaver et al. (1985) used a particle tracing technique to study the effect of the pan speed, the baffles and the pan loading on the movement in an Accela-Cota by measuring the duration of light emission from a single luminous tablet. They showed that the surface time (the time that the tablet spends on the surface) is directly related to the pan speed and the tablet bed weight. In contrast, the circulation time distribution is only affected by the pan design, i.e. the presence or absence of baffles (the mixing elements).

Many authors used the determination of the weight gain as an indicator for the mixing effect. Fourman et al. (1995) used numbered tablets to measure the individual weight gain from each tablet. They also used these marked tablets to examine the end position of each tablet in the pan related to its starting position using an Accela Cota. Chang and Leonzio (1995) examined the influence of the duration of the coating cycle by applying more film coating resulting in a higher coating level or by diluting the coating suspension but keeping the coating level constant. Prolonging the film coating process resulted in a lower coating variability among the used glass beads. A disadvantage of this method was the use of spherical glass beads, since the tablet shape also has an influence on the coating uniformity as reported by Wilson and Crossman (1997). They showed by measuring the film coating thickness at different points on the tablet that the intra-tablet coating uniformity decreased in the rank order from round, oval, capsule to large oval tablets. In most cases the coating uniformity improved with increasing pan speed.

Signorino (1994) studied the influence of the number and the arrangement of mixing devices (the baffles) by determining the weight gain after coating the tablets and the color content in the coating film.

Other methods were suggested to test the properties of the coating film, such as the determination of titanium (Harrison et al., 1991) or the determination of FD&C Blue Dye (Skultety et al., 1988). Skultety et al. established the pan speed, the amount of coating liquid applied and the spray pattern as processing parameters influencing the homogeneity of the film.

2. The Bohle Lab Coater (BLC)

In the current study a new type of a pan coater (Fig. 1), the Bohle Lab-Coater, was used (L.B. Bohle, Ennigerloh, Germany). The pan of this coater has a high length (total length: 455 mm, length of the cylindrical part of the pan, 356 mm) compared with the diameter (316 mm), thus, the length to diameter ratio exceeds 1. The pan can be divided in two equally sized zones (based on the specific airflow): the drying zone which is the back part of the pan with the inlet air supply and the spray zone which contains the spray nozzle and the outlet of the exhaust air. The pan coater has two spiral baffles working in opposite directions and this helps in mixing and transporting the tablets. These baffles help to transport the tablets, which are on the bottom of the tablet bed, from the spray zone to the drying zone. The baffles help also to transport the tablets, which are on the surface of the tablet bed, from the back part of the pan to the front. It is also possible to incline the rotation axis of the pan. This supports the transport of the tablets from the drying zone to the spray zone. Hence, the baffles, the pan speed and the inclination of the rotation axis may affect the mixing process and this, consequently, can influence the properties of the end product. The spirals used as baffles are mounted on the pan and were therefore not considered as an influence variable.

Due to the special airflow in the pan a new method was developed to evaluate the mixing efficiency in this coater. For the purpose, the temperature difference between two points in the pan (one in the drying zone and one in the spray zone) was used to examine the influence of the pan speed and the inclination of the axis of rotation on the mixing process. Predictably, a good mixing process will result in a low temperature difference. In addition, the influence of the spray rate on this temperature difference was studied. The temperature difference method was compared with simple mixing experiments in the pan using two different colored tablets of the same size and weight.

3. Materials and methods

3.1. Tablets

Round, biconvex placebo-tablets with a diameter of 11 mm were first coated with an enteric coating suspension containing Eudragit L30D (Röhm Darmstadt, Germany). Subsequently, a 5 kg batch of the coated tablets with a mean weight of 460 mg was subjected for a further study.

3.2. Experimental construction

Two temperature sensors (PTB 100) were calibrated in the range from 0 to 90 °C and then installed in the pan (Fig. 2) in order to measure the temperature of the tablet bed in the drying zone (T_D) and in the spray zone (T_S). The distance

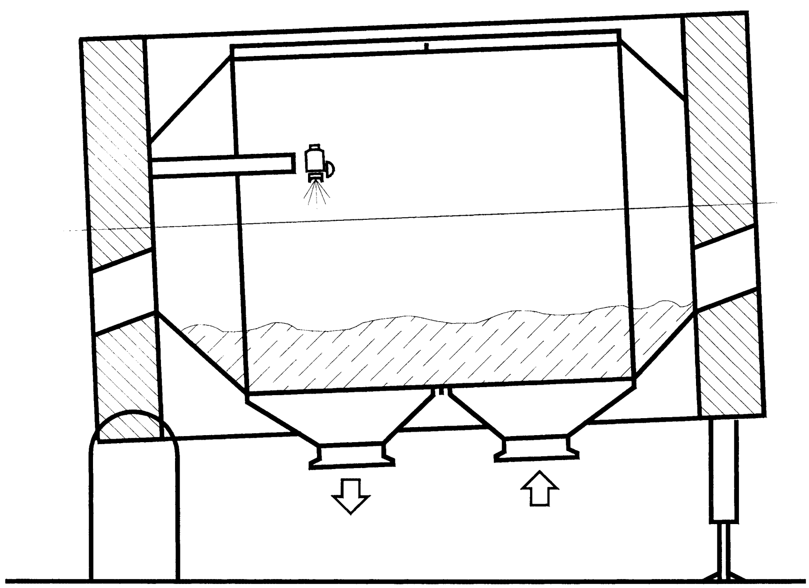

Fig. 1. Principal construction of a Bohle pan coater.

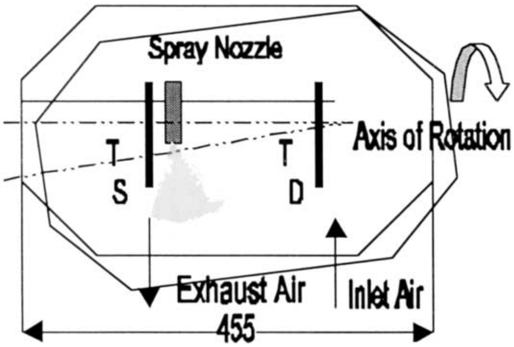

Fig. 2. Experimental set-up (• • • • inclined pan).

between the front of the pan and the sensor T_S was 90 mm, between the front and the spray nozzle 160 mm and between the temperature sensors 300 mm. The position of the sensors in the tablet bed was visually controlled. An automatic mode of the coater was used in this study dividing the process into four different steps (preheating, coating, drying and cooling). For each run the inlet air temperature and the inlet airflow rate were set to be 50 °C and 120 m^3/h, respectively. Both parameters were calibrated and could be adjusted reproducibly. The tablets were preheated to a bed temperature of 30 °C at a pan speed of 5 rpm. Demineralised water was sprayed on the tablets for 40 min in order to simulate a coating cycle. After 'coating', the tablets were dried for 20 min at a pan speed of 5 rpm. At the end of the experiment the tablets were cooled down to 35 °C. Fig. 3 displays a typical progress of such a process. The temperatures T_D and T_S were determined from the plateau reached during the water-spraying phase. For further evaluation the difference $T_D - T_S$ was calculated.

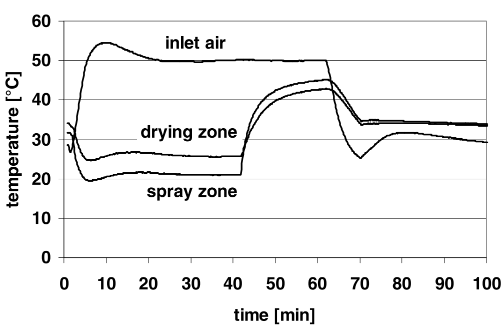

Fig. 3. Typical progress of temperatures during the experiments.

Table 1
Variables of the 3^3-design

Variable	Level		
	−1	0	+1
A, inclination of the axis of rotation (%)	0	25	50
B, pan speed (rpm)	5	20	35
C, spray rate (g/min)	5	13	21

3.3. Experimental design

A 3^3 factorial design was used to investigate the influence of the three variables (A, inclination of the rotation axis; B, pan speed; and C, spray rate) on the temperature difference and to find a functional correlation, which can describe the relation between the different variables investigated:

$$T(\mathrm{D}) - T(\mathrm{S}) = x_0 + x_A A + x_{AA} A^2 + x_B B + x_{BB} B^2 + x_C C + x_{CC} C^2 + x_{AB} AB + x_{AC} AC + x_{BC} BC$$

The experimental error for the statistical evaluation was estimated using the pure error and the higher interaction terms, which were supposed to be negligible. The variables were investigated on the levels listed in Table 1. The experiment was carried out in duplicate on the zero level.

3.4. Reference method

Simple mixing experiments were used as reference method. Therefore, 2.5 kg white tablets were filled in the back and 2.5 kg red tablets were filled in the front part of the pan. The tablets had the same size and weight as the tablets used for the temperature difference method. After mixing the tablets according to the experimental plan for one min samples of 100 tablets were taken at five different positions in the pan. The number of the white tablets was counted in each sample and the S.D. of the five values was calculated. A 3^2 factorial design (Table 3) was used to investigate the influence of the variables (inclination of the rota-

Table 2
Measured temperatures and calculated temperature difference for each run

Run	Coded variables			T_D, temperature of the drying zone (°C)	T_S, temperature of the spray zone (°C)	$T_D - T_S$ (K)
	A, inclination of the axis of rotation	B, pan speed	C, spray rate			
1	0	0	0	32.5	27.8	4.7
2	−1	1	−1	42.1	40.3	1.8
3	1	0	−1	41.9	40.5	1.4
4	−1	0	−1	40.9	38.3	2.6
5	1	0	0	33.8	30.4	3.4
6	−1	0	0	33.7	29.7	4.0
7	1	0	1	29.9	19.7	10.2
8	0	1	1	25.6	21.1	4.5
9	0	−1	−1	43.8	39.2	4.6
10	−1	−1	0	37.9	26.9	11.0
11	0	1	0	34.1	31.3	2.8
12	−1	1	1	26.6	21.6	5.0
13	−1	−1	−1	44.7	39.5	5.2
14	0	−1	0	41.4	27.2	14.2
15	0	1	−1	42.3	40.3	2.0
16	1	1	0	35.0	31.5	3.5
17	0	−1	1	38.4	19.3	19.1
18	0	0	1	31.4	20.1	11.3
19	1	−1	0	43.3	26.5	16.8
20	1	−1	1	40.6	17.9	22.7
21	0	0	−1	42.9	39.0	3.9
22	−1	−1	1	39.5	18.9	20.6
23	−1	1	0	35.3	32.2	3.1
24	0	0	0	37.9	30.3	7.6
25	1	1	1	28.0	20.8	7.2
26	1	1	−1	42.9	40.5	2.4
27	−1	0	1	31.1	20.3	10.8
28	1	−1	−1	45.5	38.3	7.2

Table 3
Variables of the 3^2-design

Variable	Level		
	−1	0	+1
A, Inclination of the axis of rotation (%)	0	25	50
B, Pan speed (rpm)	5	20	35

tion axis and pan speed) on the S.D. Both parameters estimating the mixing efficiency (difference of the temperatures and the S.D.) were compared using pareto-diagrams and surface plots. The evaluation for the temperature difference was performed for the runs with the spray rate on zero-level.

4. Results

By the virtue of the preliminary examinations, the variable levels in the experimental plan were set covering a wide range of the possible experimental space. For each run, the temperatures in the drying and the spraying zone and the temperature difference are shown in Table 2. The results were evaluated with the program Statistica® (StatSoft®).

A pareto-diagram was used to visualize the significant variables, which have influenced the temperature difference (Fig. 4). As shown in Fig. 4, the pan speed (linear and quadratic), the spray rate (linear) and the linear interaction of both affected significantly the temperature difference ($P < 0.05$). In contrast, no influence of the inclination of the rotation axis was noticed.

Another aim of the study was to postulate a functional correlation between the investigated variables and the temperature difference. This correlation can be described using the following equation (coded variables), which was also derived from the program Statistica®:

$$\begin{aligned} T(D) - T(S) &= 5.585 + 0.594A + 0.037A^2 - 4.950B + 2.504B^2 \\ &\quad + 4.461C + 0.637C^2 - 0.558AB + 0.192AC \\ &\quad - 2.908BC \end{aligned} \quad (1)$$

where A is the inclination of the rotation axis, B is the pan speed and C is the spray rate. The equation can be used to predict or interpolate the temperature difference for new settings of the three influence variables in the investigated factor space.

Fig. 5 shows a surface plot for the temperature difference in dependence of the spray rate and the pan speed. The level for the inclination of the axis was set to zero. Increasing the pan speed leads to a decrease in the temperature difference, which

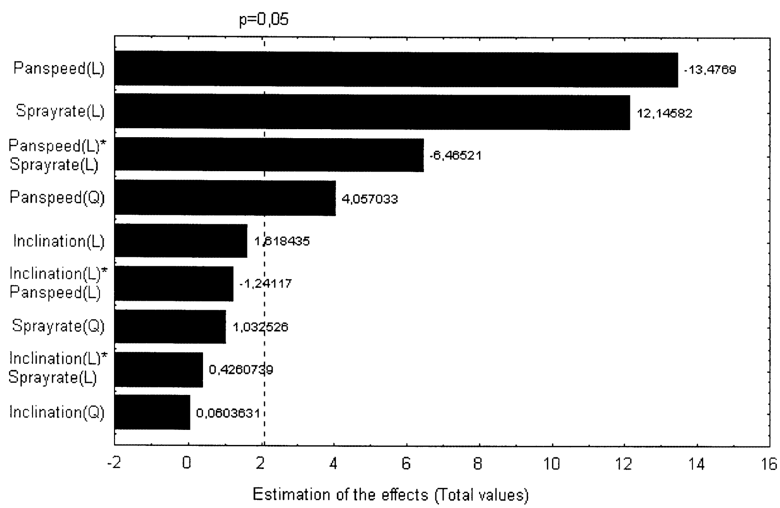

Fig. 4. Pareto-diagram for the temperature difference.

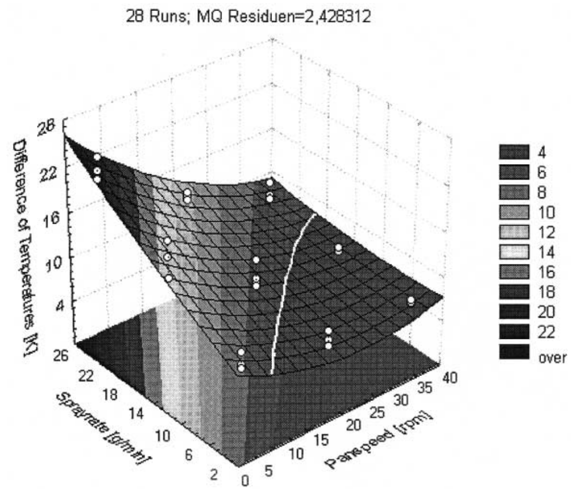

Fig. 5. Surface plot of the temperature difference (inclination of the axis of rotation on level 0).

indicates a higher mixing efficiency, whereas increasing the spray rate results in an increase in the temperature difference. However, at high pan speeds the spray rate has a negligible effect on the temperature difference. In contrast, at low spray rates altering the pan speed does not change the temperature difference. However, an increase of the spray rate at a low pan speed or a decrease of the pan speed using high spray rates leads to a remarkable increase of the temperature difference.

Table 4
S.D. of the simple mixing experiments

Run	Coded variables		S.D.
	A, inclination of the axis of rotation	B, pan speed	
1	−1	+1	1.67
2	+1	−1	41.45
3	+1	+1	4.58
4	−1	−1	37.40
5	0	0	13.86
6	0	+1	1.30
7	+1	0	12.72
8	−1	0	8.90
9	0	−1	38.00
10	0	0	10.55

The pareto-diagram of the reference method (Fig. 6, Table 4) and the pareto-diagram of the difference of temperature on the zero level of the spray rate (Fig. 7) were used to compare the new method with an conventional method. As shown in these diagrams only the pan speed (linear and quadratic) affected significantly both parameters (difference of temperatures and S.D.) ($P < 0.05$). Even the surface plots (Fig. 8 and Fig. 9) are very similar. An increase of the pan speed leads both to a decrease in the difference of the temperatures and the S.D.

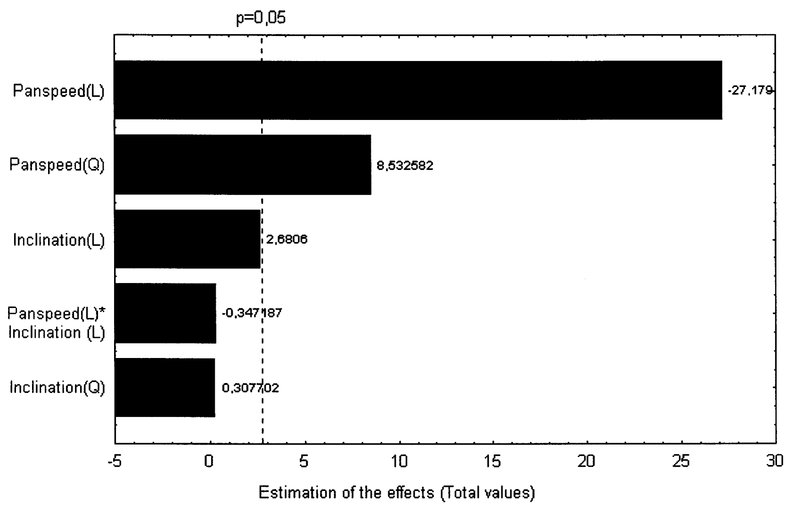

Fig. 6. Pareto-diagram for the S.D.

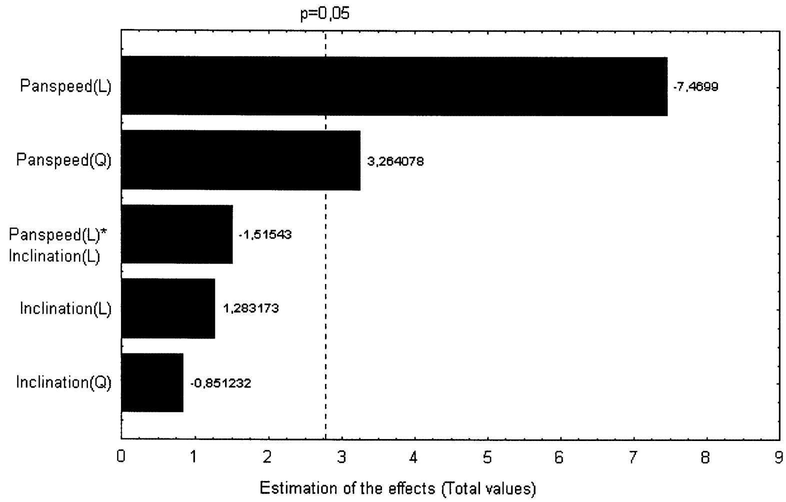

Fig. 7. Pareto-diagram for the temperature difference (spray rate on level 0).

5. Discussion

An instantaneously mixing should result in a negligible temperature difference. Thus, the best mixing behavior will be achieved at the edged area (Fig. 5). However, high pan speeds can produce attrition, which is undesired.

In this study, an influence of the inclination of the rotation axis on the temperature difference could not be observed. Using another shape or size of tablets, e.g. oval tablets, may, however, have an effect on the movement of the tablets so that the inclination of the rotation axis might affect the mixing efficiency.

A possible explanation for the increase in the temperature difference at high spray rate might be attributed to the higher energy for the evaporation of the water (at the high spray rate). Since there is no change in the inlet air temperature or the air flow, the tablets in the spray zone are much more wet and, consequently, they will be cooler compared with the tablets at low spray rates (Table 2, run 17). Using a higher pan speed can compensate this effect. In this case (high spray rate and high pan speed) the temperature measured at both sensors is lower than in other cases because wet tablets were transported faster from the spraying zone to the drying zone, and, consequently, the difference is low too (Table 2, run 8 in comparison with run 17). Regardless of the spray rate, increasing the pan speed accelerate the tablets exchange between both zones and this will result in a low temperature difference.

In contrast, at low pan speeds the tablets spend more time in each zone, so that the tablets in the drying zone become warmer and the tablets in the spray zone become cooler. Consequently, this results in an obvious increase in the temperature difference, (see runs 14 and 11 in Table 2).

The lowest temperature difference was reached at pan speeds from 10 up to 25 rpm, spray rates

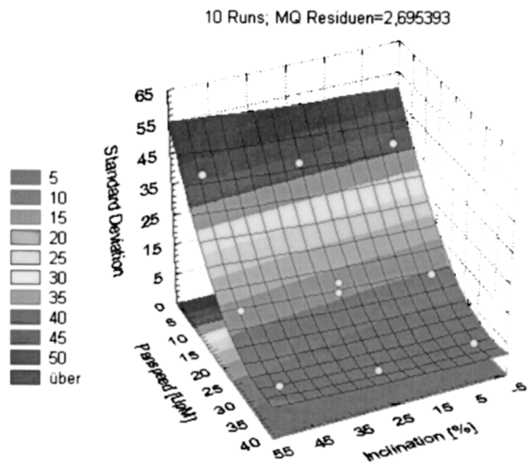

Fig. 8. Surface plot of the S.D.

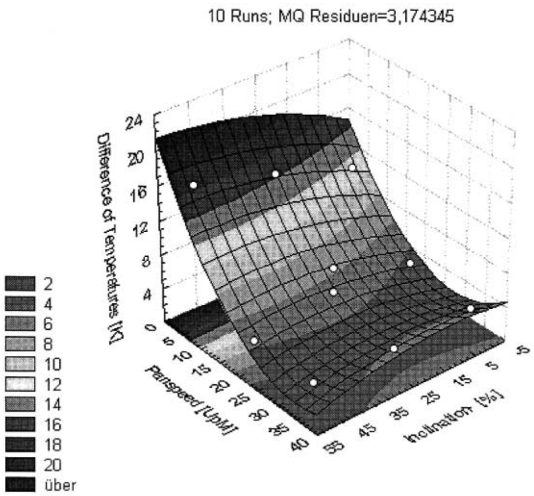

Fig. 9. Surface plot of the temperature difference (spray rate on level 0).

below 13 g/min, the inlet air temperature 50 °C, and the air flow 120 m^3/h. Pan speeds higher than 25 rpm produced attrition. No experiments were carried out to investigate whether the run time or the tablet shape may influence the temperature difference. Additionally, the method was not adapted for a scale-up process.

The comparison of the temperature difference method with the reference method showed that both methods gave the same information about the variables pan speed and inclination of the rotation axis (Figs. 6 and 7). Therefore, it is possible to replace the simple, but lengthy mixing experiment through the new method. With the help of this method, it was possible to examine the influence of the spray rate on the temperature difference. Because of this the method of the temperature difference is an improvement of the simple mixing experiments. It is now possible to make predictions about the tablet bed temperatures during a coating run in dependence of the spray rate (Table 4).

6. Conclusions

This study has demonstrated the possibility to characterize the mixing behavior in a BLC pan coater by a simple measure of the temperature difference between two points in the pan coater. It was shown that the pan speed and the spray rate clearly influence the temperature difference. An influence of the inclination of the rotation axis could not be found for the tablet shape investigated.

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