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THE MiniWiD-COATER: I. DESIGN AND EVALUATION OF A TEMPERATURE-CONTROLLED MINIATURE FLUID-BED PAN COATER

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ABSTRACT

A novel miniature laboratory-scale pan coater has been developed. Small batches of 50 to 100 g of pellets, granules, large crystalls and small tablets allow the formulation development with minimal quantities of valuable drugs and new active ingredients. Although originally it is a pan coater, the core bed will be slightly fluidized by the inlet air flow due to the small dimensions of the coating pan. This allows a rapid drying and the loss of coating materials will be negligible.

A computer was used to control the core bed temperature during the coating process by varying the spraying rate of an analytical dosing pump. Additionally, the drying air temperature can be adopted. It was possible to change the parameters during the process to optimize the operation conditions within one run. The computer program described in this article provides a constant bed temperature with a precision of ± 0.3 °C.

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In the MiniWiD-Coater, neutral pellets have been loaded with bisacodyl and then enteric-coated with aqueous dispersions of Eudragit L 30 D. Batch homogeneity and reproducibility were excellent. Friability of the cores and abrasion of the coat remained low. The loss of coating material during operation was always below 5 %.

INTRODUCTION

During the last decade several laboratory-scale film coating units have been developed. The common one was the fluid-bed technique mainly because of the small batch sizes of about 1 g and the efficient drying conditions[1,2,3]. However, the main disadvantage of this technique was the loss of coating material due to high friability and spray drying effects. On the other hand, coating pans provided a more gentle treatment of the core but tend to produce agglomerates[4] especially if used for aqueous film coating.

Therefore, it was necessary to decrease the size of the pan coater in order to minimize the loss of the coating material[5]. A capacity of about 250 ml appeared to be the smallest practicable pan size to achieve an optimum motion inside the pan.

Encouraged by the first results with organic film coating formulations, the apparatus was improved and the miniature fluid-bed pan coater was developed. The air flow was increased and the drying became more efficient so that aqueous systems could be used without agglomeration of the pellets. As a secondary effect, the core bed was slightly fluidized by the relatively high inlet air flow. Therefore, the miniature fluid-bed pan coater (MiniWiD) combined the advantages of both techniques: minimum loss of coating materials and the short processing times. Finally, the MiniWiD-Coater was equipped with a computer to automate the process and to maintain a constant temperature during the coating process. Hence the effect of coating temperature on the film quality could be examined[6].

EXPERIMENTAL

Coating apparatus

Figure 1 shows the schematic diagram of the coating device. The MiniWiD coating pan consists of a cone shaped aluminium drum with a capacity of 275 ml and an opening diameter of 51 mm. It is clamped to a motor drive and tilted at an angle of 45°.

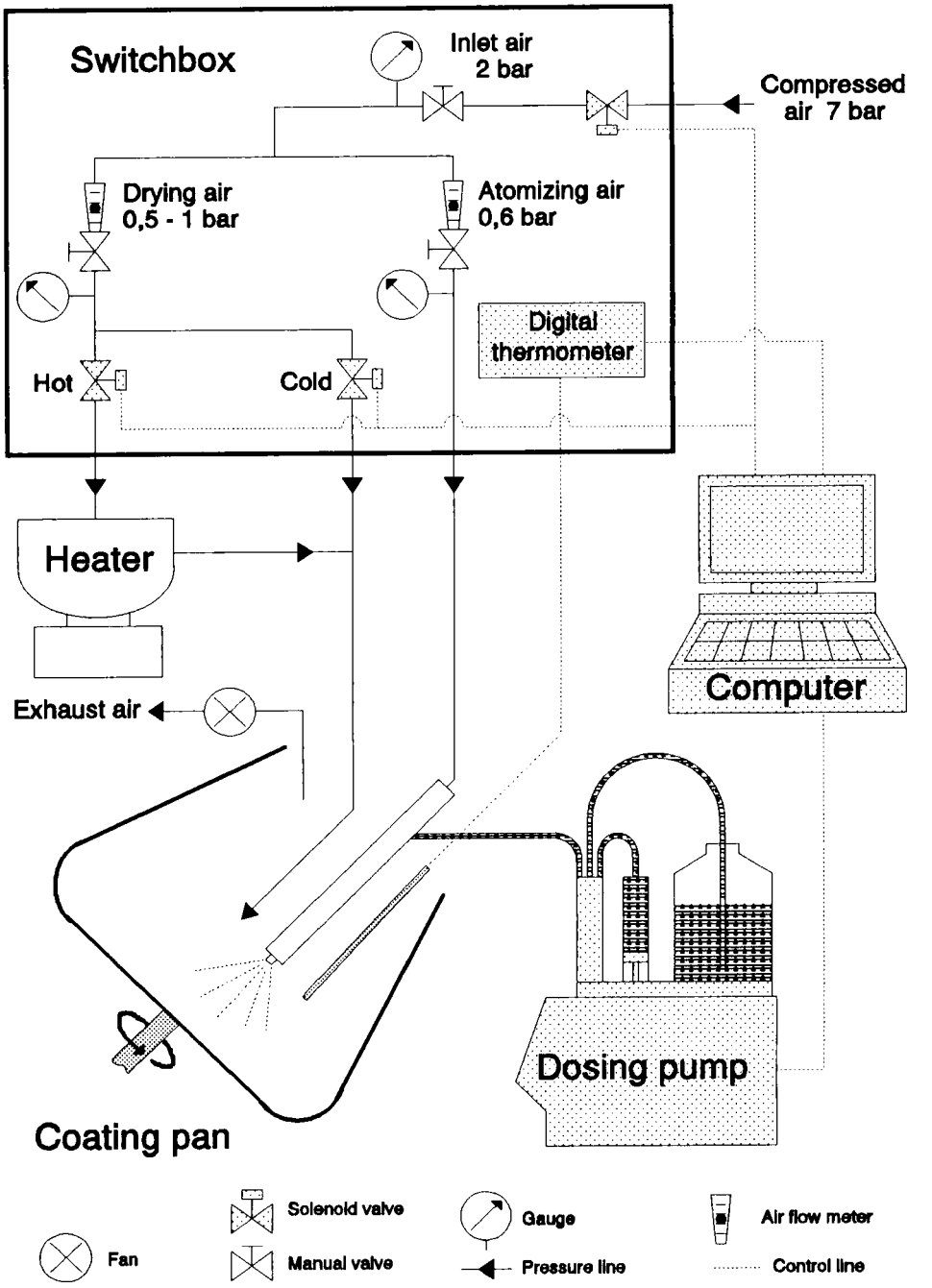

FIGURE 1
Schematic diagram of MiniWiD-Coater

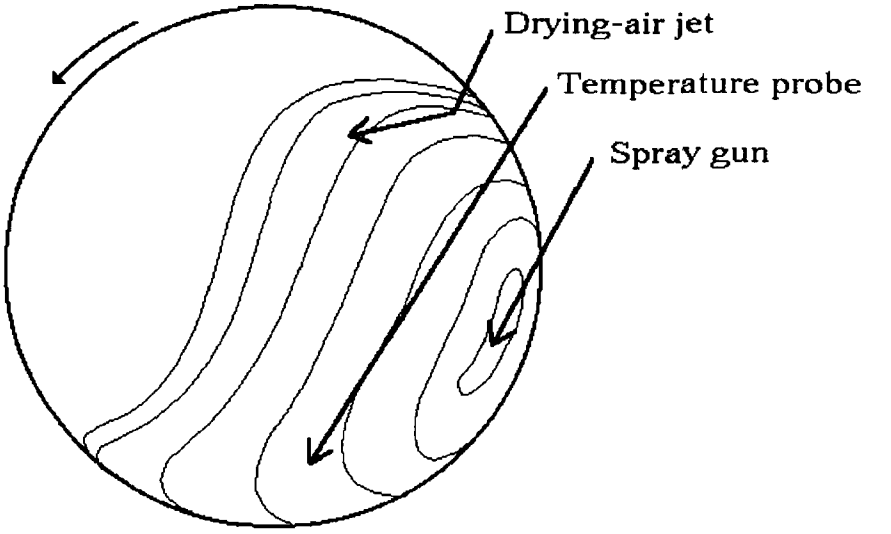

FIGURE 2
Position of jets and temperature probe

The temperature probe (Pt 100 Ω, Testoterm GmbH & Co., D-W-7825 Lenzkirch), the drying-air jet and the spray nozzle (diameter 0.8 mm, G. Schlick GmbH & Co., D-W-8630 Coburg) are located inside the pan. The outlet air is removed by an exhaust from the the top of the pan. To prevent the pellets from coming out, the jets must be positioned exactly as shown in Figure 2. While the drying-air jet is placed at the upper turning point of the tumbling bed, the spray nozzle points into the area with the slowest motion. Both jets and the temperature probe must be immersed just a few millimeters into the core bed. It is important to maintain always the same positions, especially for the probe, to get reproducible temperature results. To achieve an exact low spraying rate a dosing pump with a microprocessor (Dosimat 665, Deutsche Metrohm GmbH & Co., D-W-7204 Filderstadt) is used to supply the coating fluid.

Compressed air of 7 bar acts as an air supply and is controlled by solenoid valves. Inside the switchbox the inlet air is manually reduced to 2 bar and then devided into a drying and an atomizing air line. The different air volumes can be controlled by gauges and air flow meters and must be adjusted by hand. Before leaving the switchbox, the drying air is split again: one half is heated in a copper coil tube placed inside a hot glycerol bath, the second half is left at room temperature. By means of two solenoid valves both lines can be opened and closed individually, and the drying air may either become hot, warm or cold.

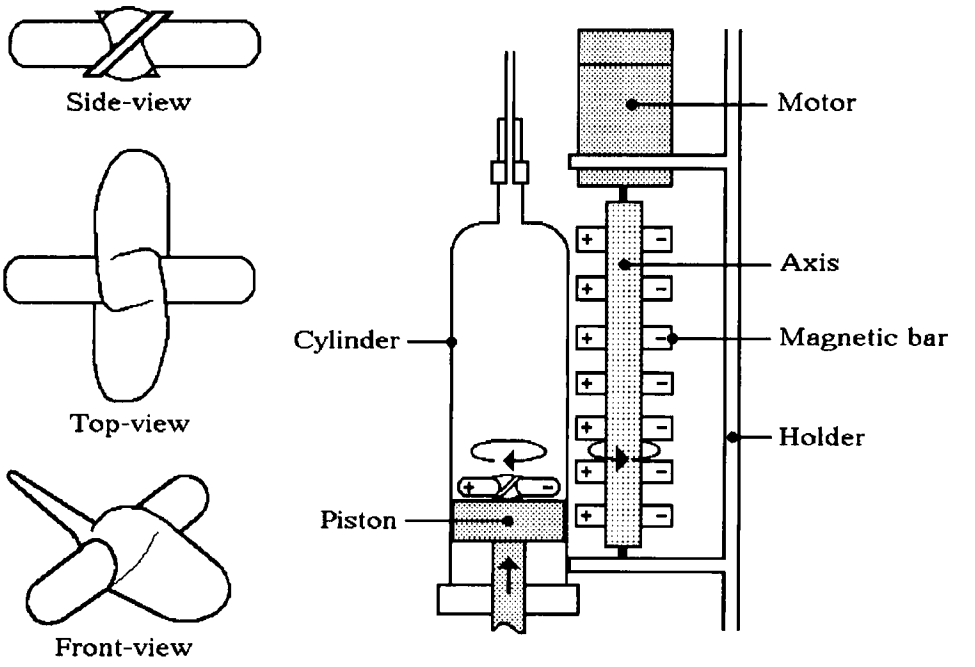

FIGURE 3
Magnetic stirrer for the glass cylinder of dosing piston pump

The computer (HP 86, Hewlett-Packard, Corvallis, OR 97330, USA) is equipped with a 5.25-inch disc drive, a random access memory (RAM) of 128 KB, a monitor and a printer. It communicates with the digital thermometer and the dosing pump via serial interfaces (RS 232) and is connected with the three solenoid valves to control the compressed air.

Due to the small size of the coating unit, aqueous dispersions could no longer be supplied by a peristaltic pump. The flow rate became very slow and the shearing forces caused latex systems to coagulate. Therefore, a piston pump with a 50-ml-glass-cylinder is used. The volume is large enough so that the cylinder must be filled only once or twice during the whole process and the dosing becomes nearly continuous. To prevent sedimentation within the glass cylinder, a magnetic stirrer has been constructed. As shown in Figure 3, a propeller-shaped stirring bar is placed inside the glass cylinder on top of the piston. Beside the cylinder, 7 magnets are fixed in a line over each other, the positive and negative poles pointing to the same side forcing the magnetic fields to overlap. The axis is driven by a speed controlled motor direction.

Computer program

The program consists of three main parts (Parameter, Process and Protocol) which can be selected by menus (Figure 4). After starting the program, the user has to set operating parameters such as core bed temperature, amount of coating material, minimum and maximum spraying rate, regulation step and postdrying time. For the final documentation, questions regarding the coating formulation, batch size, air pressures and inlet air temperature must be answered. Then the process can be started beginning with a check on all the manual operations and subsequently turning over to automatic control of the coating operation.

Each coating process consists of 3 main phases: preheating, continuous spraying and postdrying. At any time the program can be interrupted either to change a parameter or to stop spraying or to stop the process. Every action will be recorded and can be monitored on the screen.

At the end of the process, the procedure can be reconsidered by means of a protocol displayed on the monitor or printed out, and finally all these data can be stored on a disc.

Temperature control

During the process, the core bed temperature will be controlled by the computer which can adjust the spray rate and the air temperature in order to keep the set value. The control circuit is shown in Figure 5. Every two seconds, the actual bed temperature will be send to the computer and the set point deviation e will be calculated. The computer compares the actual temperature with former values of e and then adjusts the values of y_1 (spraying rate) and y_2 (air temperature).

At the beginning (preheating) and at the end (postdrying) of a process and during the refill of the dosing pump, only the drying-air will be used to regulate the core bed temperature. Below the set value hot air will be supplied and above it cold air will be used.

As soon as the core bed temperature rises to 96 % of the set value (dosing limit), the dosing pump will start with a preselected spraying rate (Figure 6). The spraying rate will gradually increase or decrease until the set value is reached. The regulation range for the dosing pump has previously been divided into at least 10 steps of equal sizes. According to the volatility of the liquid used, the regulation steps have to be higher with organic solvents than with aqueous dispersions to achieve the same effect. After each change of the spraying rate the computer waits at least 10 s because the temperature needs some time to react. Furthermore, a delay range of ± 1,6 % is defined to slow down the regulation activity around

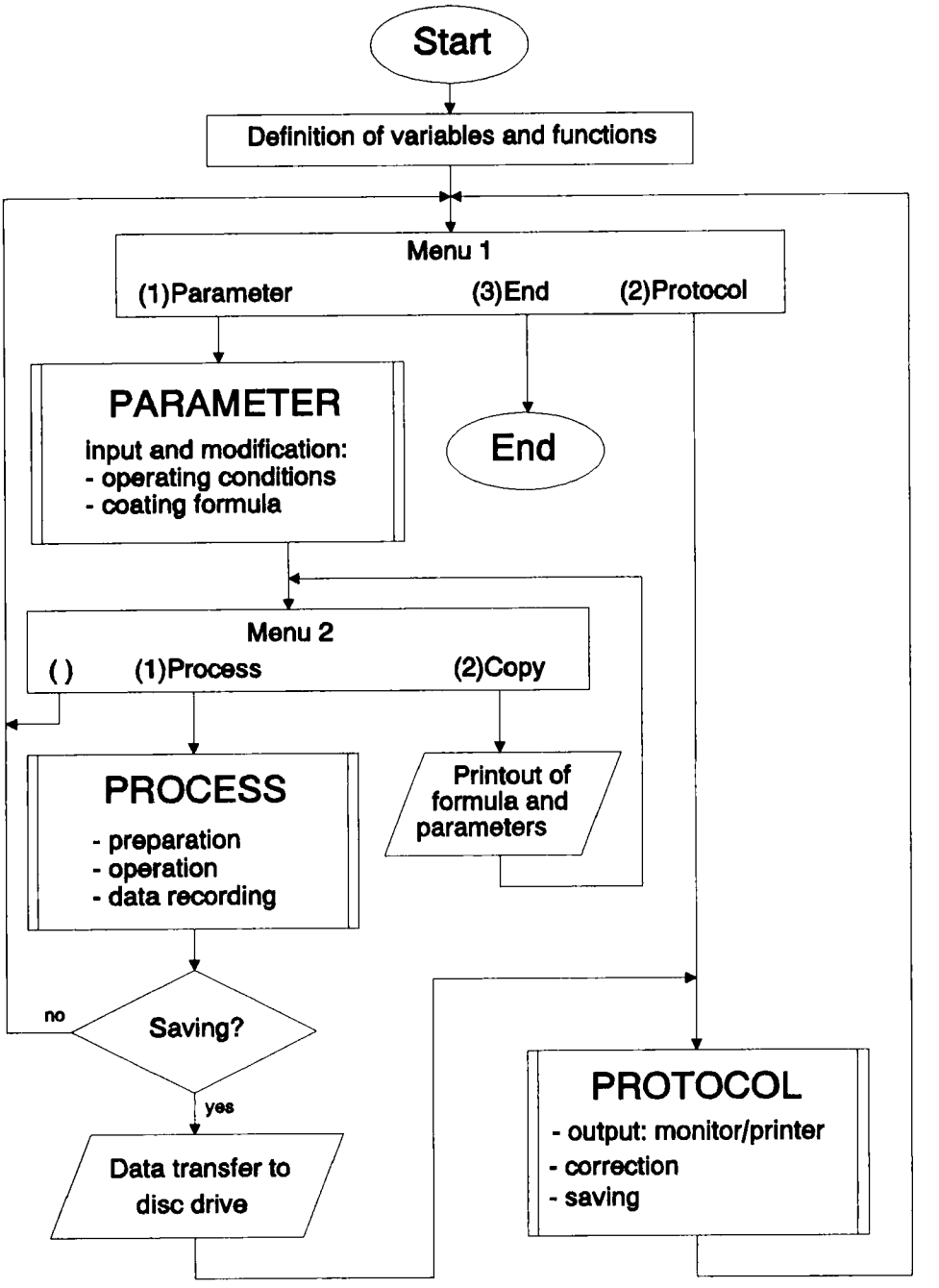

FIGURE 4
Flow chart of computer program for the MiniWiD-Coater

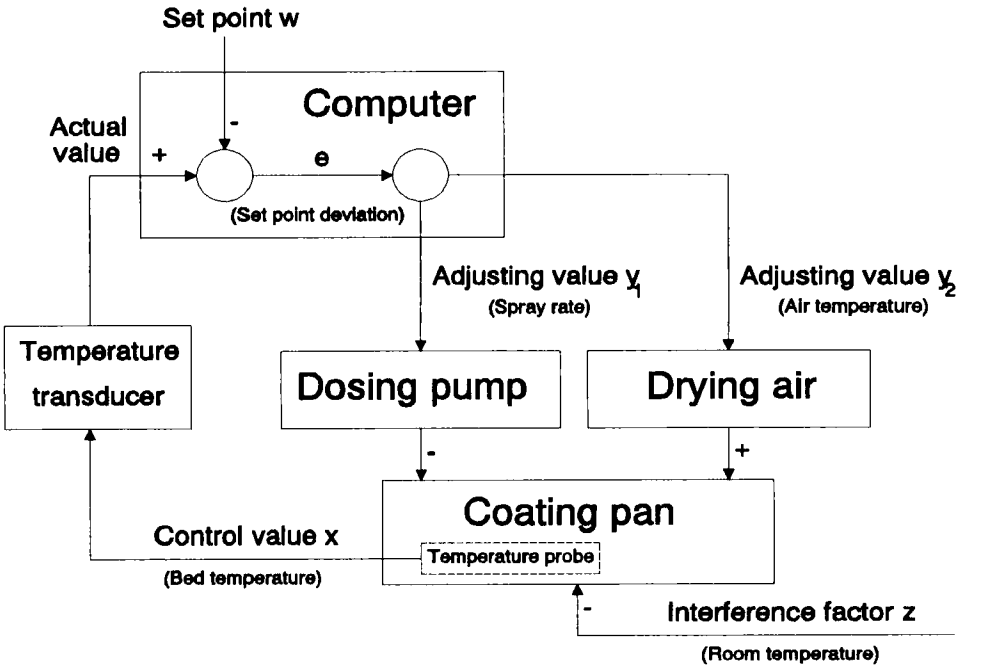

FIGURE 5
Block diagram of the control circuit of the MiniWiD-Coater

the set point. Whenever the bed temperature drops below the dosing limit, the spraying will be stopped until the temperature rises again.

On the other hand, the drying air will be used to compensate the increase in temperature of 4 % or more above the set value. In this case the drying air will first turn to warm (warm air limit) and then to cold (cold air limit) until the temperature drops again. The drying air can also be turned to hot in reverse order. All these regulations are automatically controlled by the computer.

Materials

Neutral pellets (90 % between 710 to 850 μm in diameter, Hanns G. Werner, D-W-2082 Tornesch); bisacodyl (Dr. K. Thomae GmbH, D-W-7950 Biberach); poly(ethylacrylate, methacrylic acid) 1:1 (Eudragit L 30 D, 30 % aqueous dispersion, Röhm-Pharma GmbH, D-W-6108 Weiterstadt); dibutyl phthalate (DBP, Dr. T. Schuchardt & Co., D-W-8011 Hohenbrunn); polysorbate 80 (Tween 80, Atlas-Chemie, D-W-4300 Essen); microfine talc (Norwe-

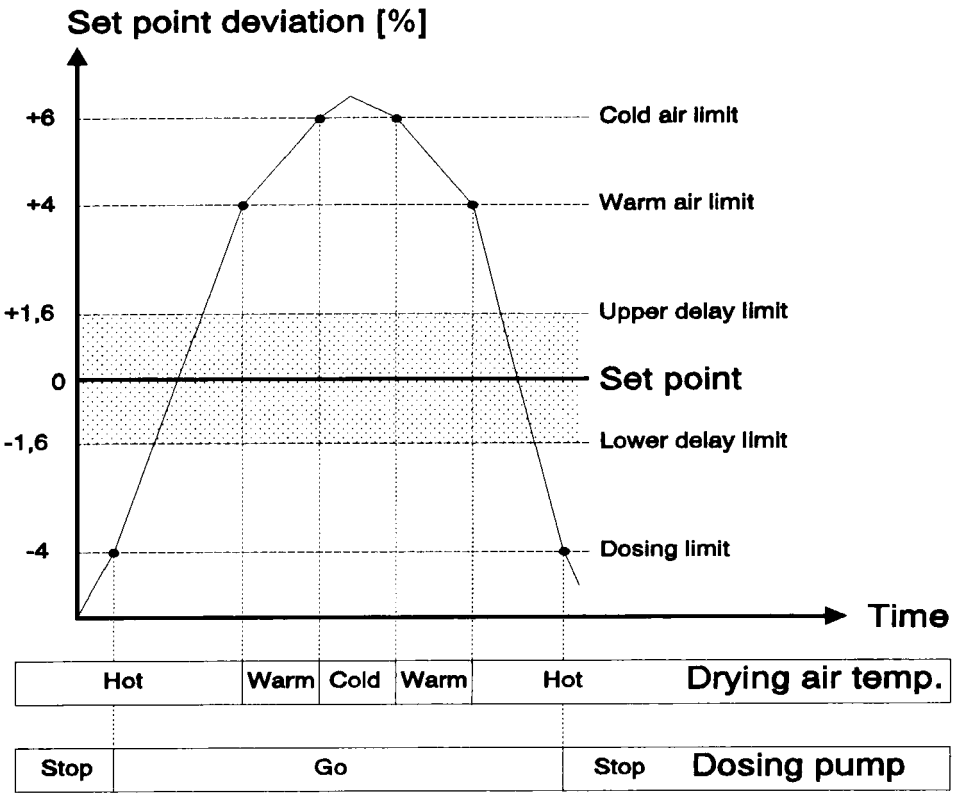

FIGURE 6
Regulation of the bed temperature during the coating process

gian Talc Deutschland GmbH, D-W-6483 Bad Soden-Salmünster); acetone and destilled water were used.

Preparation of pellets

Bisacodyl was dissolved in acetone, diluted with water and sprayed onto neutral pellets. Six 100-g-batches of bisacodyl pellets, all prepared on the same day, were combined to one batch and then coated with Eudragit L 30 D using 10 and 20 % of dibutyl phthalate (DBP) as plasticizer. Table 1 shows the formulations and the coating parameters for the different processes. Each film coating formulation was applied at 3 different core bed temperatures ranging from 25 to 45 °C. To achieve this the heater temperature had to be raised from 60 to 125 °C to produce drying-air temperatures between 52 and 95 °C. The postdrying phase

TABLE 1
Formulas and Coating Parameters of Spraying Systems

Formula		1	2	3
Bisacodyl		5.3 g	-	-
Eudragit L 30 D		-	50.00 g	50.00 g
Dibutyl phthalate		-	1.50 g	3.00 g
Polysorbate 80		-	0.40 g	0.40 g
Talc		-	0.75 g	0.60 g
Water		9.6 g	40.60 g	40.60 g
Acetone		69.2 g	-	-
Solids content	[% (w/w)]	6.30	24.40	24.40
Density	[g/ml]	0.84	1.08	1.07
Batch size	[g]	100	50	50
Volume of spray liquid	[ml]	80	60	60
Min. spray rate	[ml/min]	1.00	0.30	0.25
Max. spray rate	[ml/min]	2.20	0.60	0.52
Regulation step	[ml/min]	0.05	0.01-0.02	0.01-0.02
Bed temperature	[°C]	25	25/35/45	25/35/45
Postdrying time	[min]	0.5	5	5/3/1
Postdrying temp.	[°C]	25	25/35/45	25/35/45
Heater temperature	[°C]	70	60/90/125	60/90/125
Atomizing pressure	[bar]	0.50	0.50	0.50
Drying-air pressure	[bar]	0.65	0.70-0.85	0.65-0.80
Drying-air temperature	[°C]	58	52/73/95	52/73/96

was omitted when bisacodyl pellets were produced (formula 1) because the solvent evaporated quickly and abrasion of bisacodyl could thus be minimized.

Drug content

A sample of 0.5 g of pellets was withdrawn just before the enteric coat was applied and assayed spectrophotometrically at 264 nm in 0.1 N hydrochloric acid against a blank. The drug content was calculated from a calibration curve obtained by linear regression of 8 different bisacodyl concentrations and expressed in terms of percentage of final pellet weight.

Coating quantity

Before and after each coating process, the exchange unit of the dosing pump was weighed to determine the amount of liquid sprayed onto the pellets. Afterwards, the solids content was examined by drying an aliquot of 20 g of the spray liquid, and the amount of dry

TABLE 2
The Loading of Pellets with Bisacodyl

Run No.		1	2	3	4	5	6
Mean bed temp.	[°C]	25.06	25.02	25.04	25.04	25.00	25.05
Stand. deviation	[°C]	0.30	0.25	0.22	0.27	0.29	0.33
Min. bed temp.	[°C]	24.2	23.9	23.9	24.0	23.9	23.8
Max. bed temp.	[°C]	25.8	26.9	27.1	26.7	27.6	26.7
Spray rate	[ml/min]	1.958	1.768	1.768	1.880	1.793	1.985
Processing time	[min]	44.67	47.18	46.90	44.05	46.60	41.73
Spray liquid	[g]	67.40	67.49	67.42	67.32	67.35	67.28
Coating quantity	[g]	4.25	4.25	4.25	4.24	4.24	4.24
Weight increase	[g]	4.00	3.91	3.84	3.96	4.00	3.99
Loss of coating	[%]	5.9	8.0	9.6	6.6	5.6	5.9

substance applied (coating quantity) was calculated. The loss of coating was calculated as the difference between coating quantity and the increase in pellets weight and is expressed in terms of percentage of coating quantity.

Agglomerates

At the end of the coating process, the pellets were passed through a sieve with a mesh size of 1.0 mm. The remaining agglomerates were weighed and the amount was expressed as percentage of the final pellet weight.

RESULTS AND DISCUSSION

The reproducibility of the system was checked by repeating the experiments 6 times. In Table 2 the results of pellets with bisacodyl are shown. The mean bed temperatures differed slightly from each other and the standard deviation was very small ranging from 0.22 to 0.33 °C. Peak values of 2.7 °C only appeared for a short time and were mainly caused by refilling of the dosing cylinder.

Although bisacodyl was sprayed onto the surface without a binder, the friability of the pellets and the abrasion of the drug remained reasonably small. Therefore, all batches were

TABLE 3
The Coating of Bisacodyl Pellets with Eudragit L 30 D

Plasticizer		10 % DBP			20 % DBP		
Run No.		1	2	3	1	2	3
Mean bed temp.	[°C]	25.01	35.01	45.01	25.02	35.02	45.01
Stand. deviation	[°C]	0.20	0.25	0.24	0.16	0.20	0.23
Min. bed temp.	[°C]	24.2	33.8	43.1	24.1	34.4	43.3
Max. bed temp.	[°C]	26.0	36.4	46.2	25.7	36.4	45.8
Spray rate	[ml/min]	0.417	0.415	0.426	0.406	0.425	0.429
Processing time	[min]	111.2	115.3	111.9	116.6	111.3	111.0
Spray liquid	[g]	48.79	48.81	48.71	48.36	48.32	48.27
Coating quantity	[g]	11.90	11.91	11.89	11.80	11.79	11.78
Weight increase	[g]	11.87	11.80	11.60	11.90	11.76	11.44
Loss of coating	[%]	0.3	0.9	2.4	-0.8	0.3	2.9
Agglomerates	[%]	-	0.1	2.2	-	0.3	3.1
Drug content	[%]	3.81	3.83	3.87	3.94	3.94	3.90

combined into one single batch. The following operating conditions were important:

- short preheating time of 15 s
- low bed temperature of 25 °C
- short postdrying time of 30 s
- short refilling time the cylinder (1 min)
- high spraying rate

Table 3 shows the results of aqueous film coating with Eudragit L 30 D using two different concentrations of DBP. In spite of varying bed temperatures the press data were very similar and only marginal differences could be detected. As a result of the increased processing time, the standard deviation was reduced. While the coating quantity remained always the same, the loss of coating increased at higher temperatures possibly due to rapid drying of the droplets. It was noticed that increasing coating temperatures led to more agglomeration of pellets. This might indicate a growing tackiness of the film.

CONCLUSIONS

The computerized MiniWiD-Coater is suitable for the application of both organic solutions and aqueous dispersions onto pellets under reproducible conditions. Batch homo-

geneity seems to be excellent. This permits the production of films at different temperatures and therefore the effect of temperature on the film quality can be examined.

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